RISK FACTORS OF POSTOPERATIVE DELIRIUM AFTER HIP FRACTURE REPAIR

by
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ABSTRACT

A statement of the problem: Postoperative delirium is associated with poor functional recovery, institutionalization and high cost of medical expenditure. The objectives of the study were to i) identify risk factors of postoperative delirium by performing a systematic review; ii) develop a clinical prediction model of postoperative delirium; iii) determine whether cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) are associated with postoperative delirium. All of the objectives were explored in hip fracture population.

Methods: Systematic review was conducted using prospective observational studies with estimation of association between preoperative risk factors and incident postoperative delirium in multivariable models. Risk factors identified as significant predictor of postoperative delirium in a hip fracture dataset of 429 individuals with acute hip fracture were combined with the risk factors identified from the systematic review. A clinical prediction model was developed and internally and externally validated. CSF was collected from individuals with hip fracture enrolled in a clinical trial and analyzed for biomarkers of Alzheimer's disease (AD).

Results: Search yielded 6,380 titles and abstracts from electronic databases and 72 titles from hand searches, and 10 studies met inclusion criteria. Cognitive impairment most consistently remained statistically significant after adjusting for other risk factors in multivariable models, followed by BMI/albumin and multiple co-morbidities. The independent variables for predicting postoperative delirium in the prediction model were age, gender, dementia, Parkinson's disease, American Society of Anesthesiologists

(ASA) Physical Status Classification, and albumin level. Our postoperative delirium RPM had discrimination (receiver operating characteristic ROC curve) of 0.72 with external validation ROC of 0.62. There was no association of CSF AD biomarkers with postoperative delirium.

Conclusions: Cognitive impairment was identified as one of the strongest risk factors for postoperative delirium in hip fracture population. Risk stratification may be performed using the risk predication model (RPM) developed in hip fracture population, but the discrimination ability of the RPM in external validation was less than optimal. Although cognitive impairment was strongly associated with postoperative delirium, CSF AD biomarkers were not associated with postoperative delirium in a small group of hip fracture patients.

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CHAPTER I.

INTRODUCTION

As the populations in the United States (U.S.) and other countries age, the number of older adults with hip fractures will continue to rise. It is estimated that the annual hip fracture rate in the U.S. alone is close to 300,000, and is expected to exceed 6 million world-wide by 2050 (1, 2). Hip fracture has the highest incidence and associated costs of all fractures that occur among adults 65 years and older, with estimated 2.9 billion dollars in Medicare costs (3). It is also associated with multitude of complications including prolonged rehabilitation, loss of independence, and mortality (4), with a recent study showing a 36 % mortality at 6 months among nursing home residents (5).

One of the major complications of hip fracture is delirium, with an incidence of up to 54 % in this population (6). The new diagnostic criteria for delirium in the Diagnostics and Statistical Manual (DSM) V include a) disturbance in attention and awareness that develops over a short period of time that is a change from baseline and fluctuates during the course of a day, ii) additional disturbance in cognition, iii) the disturbances in attention and cognition are not better explained by another preexisting condition, and iv) the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple etiologies (7). As the diagnostic criteria suggest, potential etiologies for delirium can vary, and often they are due to multiple etiologies.

Delirium is a complication which costs upwards of 6.5 billion dollars in Medicare hospital expenditures (8), and is associated with poor functional recovery (9) and institutionalization (10). However, delirium is a preventable condition with available effective hospital-based delirium prevention approaches (11, 12). Therefore, prioritizing and targeting patients who are at higher risk of delirium will help clinicians in identifying high risk patients for close monitoring and implementation of delirium preventive strategies including proactive geriatrics co-management at all stages of perioperative care. In addition, stratification of high risk patients would enable efficient design of future intervention studies as well as cost effective delivery of these interventions (8, 13).

In order to identify those who are at high risk of postoperative delirium, several systematic reviews have examined preoperative delirium risk factors in non-cardiac surgery (14), or in mixed orthopedic surgeries including elective knee and hip surgeries (6). However, the incidence of delirium is usually higher after hip fracture surgery (5-53.3 %) compared to elective hip surgery (3.6-28.3 %) (6). This suggests that the type of surgery and underlying condition may result in different magnitudes of delirium risk associated with a risk factor (14). Nevertheless, systematic reviews focusing on hip fracture are lacking, despite its frequency, costs, and clinical relevance. In addition, many of the existing studies have been limited by including patients with prevalent delirium and focusing solely on preoperative risk factors from bivariate analysis, which make it difficult to identify independent risk factors for incident delirium following surgery.

One of the ways to preoperatively determine the risk for postoperative delirium is by using risk prediction models (RPMs) which are partly built on the risk factors identified from systematic reviews. RPMs allow preoperative risk stratification of patients undergoing surgery, so that interventions can be targeted towards high risk population. In the current environment where medical resources are often limited, targeted interventions will allow optimization of resource allocation by delivering cost-effective care in a timely manner. Recently, there has been a systematic review demonstrating the effectiveness of a non-pharmacological delirium prevention method Hospital Elder Life Program (HELP) (12) as well as a potential pharmacological delirium prevention treatment such as ramelteon (15) among others. As more delirium prevention methods are developed in the future, development and incorporation of RPMs in research could potentially increase the statistical power by enriching the study population as well as facilitating implementation of delirium prevention methods in clinical practice.

There are many postoperative delirium RPMs that have been developed over the years, but they vary in terms of the study population of interest and validation procedures, with few studies completing internal and external validations (16). A recent systematic review of postoperative delirium RPM found that of the 37 RPMs that met the review criteria, only three were validated internally, and four were validated externally (16). Among the four externally validated RPMs of postoperative delirium, only one study was an external validation in hip fracture population (17). As this study was a validation of a RPM that was originally developed on non-surgical population (18), it would be important to examine if the RPM that is developed from a hip fracture population would be different in terms of risk factors and provide better estimates of postoperative delirium.

In addition to identifying clinical risk factors of postoperative delirium and developing RPMs based on these risk factors, there has been growing interest in investigation of biomarkers to assess risk of postoperative delirium (19). As underlying cognitive impairment due to a neurodegenerative disease is thought to be an important risk factor for postoperative delirium, there has been an effort to investigate biomarkers of a neurodegenerative disease such as Alzheimer's disease (AD). AD is one of the most common causes of dementia in the U.S., and thought to be linked to delirium (20).

The pathology of AD is characterized by deposition of amyloid plaques and neurofibrillary tangles (NFT) along with degeneration of synapses and neurons (21, 22). Amyloid plaques are composed of extracellular deposits of the amyloid-beta 42 ($A\beta_{42}$) and 40 ($A\beta_{40}$) peptides (23), and NFTs are composed of intracellular cytoplasmic deposits of abnormally phosphorylated tau protein (24). More recently, the knowledge that AD pathology begins many years prior to the clinical manifestation of dementia (25-27) has led to the new AD diagnostic criteria which encompasses three different stages including preclinical (28), mild cognitive impairment (MCI) (29) and AD dementia (30).

The new diagnostic criteria recommend incorporation of specific CSF biomarkers in diagnosing underling AD process, including decreased levels of amyloid-beta 42 ($A\beta_{42}$), increased levels of tau (total tau, phosphorylated tau $_{181}$) and increased tau/$A\beta_{42}$ ratio, which appear to be sensitive to the earliest stages in AD pathology (31, 32). They are widely used in research for diagnosis of AD (30), especially in the more heterogeneous pre-dementia stages since they confirm the brain presence of AD pathology (28, 29).

The goal of the overall study is to examine potential preoperative clinical risk factors for delirium after hip fracture surgery by conducting systematic review, focusing on studies that examined incident delirium after surgery and investigated independent association of risk factors with postoperative delirium in multivariable models. After the identification of the clinical risk factors, a RPM based on a hip fracture population will be developed, then internally and externally validated.

In addition to identifying the clinical risk factors and building a RPM, we will also determine whether preoperative CSF levels of AD biomarkers $A\beta_{42}$, tau (t-tau, p-tau181$_{181}$) and tau/$A\beta_{42}$ are associated with occurrence of postoperative delirium in patients undergoing hip repair surgery.

CHAPTER II

PREOPERATIVE RISK FACTORS FOR POSTOPERATIVE DELIRIUM FOLLOWING HIP FRACTURE REPAIR: A SYSTEMATIC REVIEW

METHODS

Literature Search Strategy

We searched PubMed, EMBASE, PsycINFO, CINAHL, and Cochrane Library from inception of database to April 15, 2013 without any language restrictions. We also searched for unpublished dissertations using Proquest Dissertations and Theses, and WorldCatDissertations. We hand-searched 15 journals and supplemental sections of five journals limited to issues published in 1990 or later (6). Complete list of hand-searched journals, journal supplements and search terms for electronic and hand-searches can be found in Appendix 1.

Study Selection

The title and abstract of each article were independently reviewed by two reviewers. Studies were included for the following criteria: i) prospective observational study; ii) adult patients (≥18 age) who underwent hip fracture surgery; iii) provided data on incident postoperative delirium by excluding individuals who had delirium before surgery; iv) included data on a concurrent, non-historical group of patients who underwent hip fracture surgery, but did not develop postoperative delirium; v) delirium assessed using Diagnostic and Statistical Manual of Mental Disorders (DSM) III or IV edition, or DSM derived criteria such as Confusion Assessment Method (CAM), Delirium Symptom Interview, Delirium Rating Scale, or Neelon and Champagne (NEECHAM) Confusion Scale; vi) risk factors examined in multivariable model.

Studies were excluded for the following criteria: i) randomized controlled trials (clustered and cross-over), retrospective studies (cohort and case-control), cross-sectional studies, or review articles; ii) Mixed study population: data on patients who underwent hip fracture surgery could not be separated from other patients (e.g. other surgical/medical patients or elective hip surgery patients); iii) data on incident delirium could not be separated from prevalent (present on admission) delirium; iv) did not examine at least one preoperative risk factor for postoperative delirium; v) no estimate of association between risk factors and postoperative delirium; vi) animal study; vii) foreign language (non-English). Studies with only bivariate results were excluded, since our goal was to examine studies with adequate control for confounding. Included and excluded studies are reported using the PRISMA systematic review protocol (33).

<u>Data Extraction and Management</u>

Reviewers divided into two groups (EO and ML, EO and TF), and double data extraction and double data entry were conducted. Any discrepancies were resolved through discussion and consensus agreement. Quality assessment was completed by two independent reviewers based on pre-defined criteria. Data from Lee et al. (34) encompassed some of the data presented by Zakriya et al. (35) and Sieber et al. (36). The latter two studies were not incorporated into the data presented in Tables II.3 and II.4. However, they were included in data extraction for other information in this review (Table II.2). A variable was categorized as significant (S) in bivariate models if it met the cut-off p-value as determined in each study (Table II.3). P-value of 0.05 was chosen for significance in multivariable models (Table II.4).

RESULTS

Study Characteristics

Initial search yielded 6,380 titles and abstracts from the electronic databases and 72 titles from hand searches. After duplicates were removed, 4,786 abstracts were reviewed for initial screening, and 162 for the next stage of review. After inclusion and exclusion criteria were applied, 10 full text articles, including one dissertation, were chosen for detailed analysis (Figure II.1). Reasons for exclusion are listed on the flow diagram.

Postoperative Delirium Assessment

The incidence of postoperative delirium ranged widely from 13 % (37) to 55.9 % (38), and were identified by DSM-IV or DSM derived instrument. Among studies that specifically stratified preoperative risk factors by baseline cognitive function, postoperative delirium incidence was consistently higher in those who had cognitive impairment compared to those who did not (Table II.2). Some studies specifically excluded those with diagnosis of dementia (35, 37).

Optimal Time Period of Delirium Detection

One of the interesting questions to ask is if more frequent postoperative delirium assessments contribute to higher delirium incidence, whether longer postoperative assessments also result in higher delirium incidence. Although not all articles reported the incidence of delirium by postoperative days, studies reported the highest incidence on the first and second postoperative day. Bjoro and Goldenberg et.al reported 91.2 % and 78.4 % of all postoperative delirium occurred between postoperative day 1 (POD1) and 3 (POD3), respectively (39, 40). Nie et al. also reported detecting 93.75 % of the delirium occurrence in between POD 1 and POD4 (37).

Delirium Severity and Duration of Delirium

Delirium severity was assessed in only two studies: one (40) used the MDAS, and the other (37) used the Delirium Rating Scale–Revised-98 (DRS-R-98) (41). Four studies reported delirium duration, with two reporting delirium of one day duration in 39 % (40) to 75 % (37) of cases. One study (38) reported an overall mean of 2.9 days for delirium duration, and another (42) reported duration ranging from one to nine days, with overall mean of 3 days.

Preoperative Risk Factors of Postoperative Delirium

Cognitive Impairment

Mini-Mental Status Examination (MMSE) (43) was the most widely used tool for cognitive evaluation. Additional approaches to quantify preoperative cognitive state were the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF) (44) or the Set Test (45). One study used an unvalidated simple four item screen to define preoperative cognitive status (46). Methods of classifying cognitive impairment status varied among studies, ranging from those that relied on cognitive testing tools (34-38, 40, 47) to those that also used additional information such as Diagnostic and Statistical Manual-IV (DSM-IV) criteria (39), incorporated evaluation by clinicians (34, 36, 47), or information from medical records for additional history of dementia diagnosis (34, 36, 46).

In seven studies, cognitive impairment was a significant risk factor of postoperative delirium in the bivariate models. It remained statistically significant in six out of the eight studies in the multivariable models. Among those six studies, three studies reported cognitive impairment to have the largest effect sizes among all the risk factors in the multivariable models, and two studies reported it to have the second largest effect sizes (Table II.4).

Several studies further stratified the patients by cognitive status, and examined preoperative risk factors separately. In the cognitively impaired, female gender, femoral neck fracture, abnormal blood pressure, heart failure on admission, meperidine use, and low doses of opioid analgesia (parenteral morphine sulfate equivalents of < 10 mg/day) were significant preoperative risk factors in one study (46), and BMI and laboratory WBC values in another (40). A third study showed that only time between emergency department (ED) and surgery was a significant preoperative risk factor (34).

In the cognitively intact, Functional Independence Measure (FIM) score, severe pain at rest and low doses of opioid analgesia (parenteral morphine sulfate equivalents of < 10 mg/day) were significant preoperative risk factors (46), in addition to American Society of Anesthesiologist (ASA) Physical Status Classification (40). One study showed that age, male gender, Body Mass Index (BMI), and number of medical comorbidities were significant preoperative risk factors (34). As the risk factors examined in these studies did not overlap, it was difficult to draw conclusions from aggregated data. These studies also did not report whether interactions were examined in the statistical models.

Age and Gender

Among eight studies that examined age as a risk factor, six studies showed a significant association with postoperative delirium in the bivariate models (Table II.3). However, age remained significant in only two studies after adjusting for other risk factors in multivariable models, and the effect sizes were small in both studies (Table II.4). Only two out of five studies showed a significant association between male gender and postoperative delirium in the bivariate models (Table II.3), and only one remained significant in the final multivariable models (Table II.4).

Institutionalization and Functional Impairment

Among studies examining institutionalization as a risk factor for postoperative delirium, all showed significant associations in the bivariate models (Table II.3). However, none remained significant in multivariable models (Table II.4). Similarly, none of the studies that showed significant associations between functional impairment and postoperative delirium in the bivariate models (Table II.3) remained significant in the multivariable models (Table II.4). Methods of classifying functional impairment varied widely among the studies, ranging from a simple categorization as needing “help from others before admission”(42), to using more standardized tools such as activities of daily living (ADL) (34, 39, 47) to Functional Independence Measure (FIM) (46).

BMI and Albumin

Three studies examined body mass index (BMI) (34, 40, 47) and three studies examined albumin (39, 40, 47). Two that used BMI below $20kg/m^2$ as impaired showed significant association with postoperative delirium in the bivariate models (Table II.3), and remained significant in the multivariable models (Table II.4). One study that examined albumin < 3.5 g/dL also showed significant association with postoperative delirium in both the bivariate and multivariable models (Tables II.3 and II.4).

Multiple Comorbidities, Acute Medical Conditions and American Society of Anesthesiologists (ASA) Physical Status Classifications

Three out of five studies that examined multiple comorbidities found them to be significantly associated with postoperative delirium in the bivariate models (Table II.3). In two of the three this association was significant in the multivariable models as well (Table II.4).

Two studies examined acute medical conditions that required treatment upon admission including cardiovascular or pulmonary problems (42) as well as congestive heart failure or abnormal blood pressure (46). These were found to be significantly associated with postoperative delirium in the multivariable models (Table II.4).

Three out of four studies that examined American Society of Anesthesiologist (ASA) Physical Status Classification system found it to be significant in the bivariate models (Table II.3). However, one study did not incorporate ASA Physical Status Classification in the multivariable model due to collinearity (34), and the other two were not significant in the multivariable models (Table II.4).

Polypharmacy

Similar to the categorization of multiple comorbidities, different studies used different criteria to define polypharmacy. One used > 3 medications (39), and others used > 5 medications (40, 47) to define polypharmacy. Two showed significance in the bivariate models (Table II.3), but only one retained significance in the multivariable model (Table II.4).

Vision and Hearing Impairment

Only one study examined vision and hearing impairment (42). Self- reported vision impairment was associated with delirium in both the bivariate and multivariable models (Tables II.3 and II.4). Hearing impairment, which also relied on patient self-report was not associated with post-op delirium (42).

Quality of Studies

Selection bias: 6 out of 10 studies specifically noted that consecutive patients were enrolled into the studies (34, 35, 38-40, 47). However, only 2 out of 10 compared baseline differences between those who were included in the study and those who were excluded (39, 47). There were no significant differences in age (39, 47), gender (47), morbidity (39), or lab values (39) in these studies.

Measurement error: there was variability in ascertainment of baseline characteristics. One study collected information from medical records (38). Others collected information from medical records and from a combination of patient, proxy interviews, and staff interviews (34, 37, 40, 46). The study that reported on vision and hearing impairment relied on self-report (42). None of the studies clearly stated whether outcomes were assessed by raters masked to baseline exposure/risk factors.

Although all the studies examined clinical variables in adjusted models, only two studies specifically stated that effect modifications were explored by examining interactions between variables (47) or that collinearity was checked between risk factors. (34).

DISCUSSION

This systematic review demonstrates that cognitive impairment is the most consistently significant preoperative risk factor for postoperative delirium after hip fracture surgery, followed by BMI or albumin levels and multiple comorbidities, all of which had at least two studies that were significant in multivariable models with effect sizes greater than 1.1. Although the exact underlying pathophysiology of delirium is not known, some of the leading hypotheses are similar to those proposed for neurodegenerative processes such as Alzheimer's disease and other types of dementia. One is central cholinergic deficiency representing an underlying vulnerability that predisposes individuals to delirium (48). Another is inflammation, which may play an important role both as a predisposing factor in the form of CNS inflammation as well as a precipitating factor from systemic inflammation such as infection (49). Therefore, it makes sense that in a majority of studies the most consistent risk for postoperative delirium is pre-existing cognitive impairment, and this finding is similar to previously published studies (14, 50)

Although baseline cognitive impairment is an important risk factor for postoperative delirium, cognitive assessment is often not conducted prior to emergency hip fracture repair. One reason is the perception that there is not enough time to perform cognitive testing in the preoperative setting. However, many studies, including those in this systematic review, demonstrate the feasibility of preoperative cognitive testing in emergency settings. Most studies reviewed (34-40) used MMSE, but one demonstrated that even a four-item screening questionnaire was sensitive enough to detect cognitive impairment predictive of postoperative delirium (46). Therefore, cognitive testing should become part of the standard of care for preoperative assessment for hip fracture surgery.

Another important risk factor was BMI and blood albumin levels. While low BMI and albumin levels are thought to represent poor nutritional status, they may also be reflective of inflammatory states associated with chronic disease (51). In four studies that examined either factor, postoperative delirium was associated with low BMI in two studies and low albumin in one study. As inflammation likely plays a large role in delirium pathogenesis (49), BMI and albumin may be indirect measures of systemic inflammation related to general medical conditions. In addition, individuals with low albumin may be susceptible to greater bioavailability of drugs highly bound to albumin, and therefore at greater risk of side effects including delirium (52).

In this review, while several studies reported age to be a significant risk for delirium in bivariate models, this association lost significance in all but two studies. While loss of statistical significance in multivariable models may be due to the narrow age range of subjects in these studies (53), the association between age and delirium is likely mediated by other risk factors, such as cognitive impairment.

Several studies assessed preoperative physical condition as a risk factor of delirium by examining number of medical comorbidities, acute medical conditions, and the ASA Physical Status Classification. Although disease burden is an important factor in delirium risk assessment, the studies reviewed had different ways of defining multiple comorbidities as well as acute medical conditions. It might be more informative if specific conditions thought to increase postoperative delirium (e.g. vascular risk factors) are examined separately (54).

An interesting finding is that although five studies showed a significant association between institutionalization and postoperative delirium in bivariate models, in none was this association significant in multivariable models. We see similar results with functional impairment, associated with postoperative delirium in bivariate models in five of six studies, but not in any multivariable models. One explanation is that these variables may be collinear, since most residents of skilled nursing facilities have functional impairments. However, this also demonstrates the robustness of the association between cognitive impairment and postoperative delirium, as this factor remained significant in multivariable models even though it is likely highly correlated with the aforementioned variables.

The strengths of this systematic review include the rigorous synthesis of evidence across studies, involving patients across hospitals. Important methodological advances over prior reviews are exclusion of prevalent delirium that allowed us to elucidate preoperative risk factors of incident delirium, and examination of studies that that had multivariable models enabling us to identify independent risk factors. This work will allow development of prediction models to identify high risk groups who will benefit from preventive interventions for delirium.

The limitations of this review include the small number of studies available, the different risk factors examined across each study, and the variability in measures and outcomes used. Meta-analysis of the risk factors was not performed due to the limitations of the studies, as there were not enough significant risk factors in multivariable models among the selected studies. Although examination of preoperative clinical risk factors is important in understanding underlying risk, they do not explain all the variances in the outcome of postoperative delirium. As preoperative risk factors represent predisposing vulnerability, other factors such as intraoperative and postoperative risk factors which are precipitating risk factors are also important determinants of the outcome (55).

In summary, cognitive impairment was one of the most important preoperative risk factors for delirium after hip fracture surgery, followed by BMI/albumin levels and multiple comorbidities. Given the strength of this association, a careful preoperative assessment of cognitive function would be most important in identifying those who are at the highest risk of postoperative delirium. Furthermore, future delirium intervention studies may be designed based on stratification of subjects by preoperative cognitive function.

In addition, baseline measures of BMI and blood albumin levels may be helpful in identifying those with underlying inflammatory status. While age is important, age alone should not be used to risk stratify patients, and careful assessments of cognitive function and other medical conditions should be taken into account.

Figure II.1. Flow diagram of search strategy

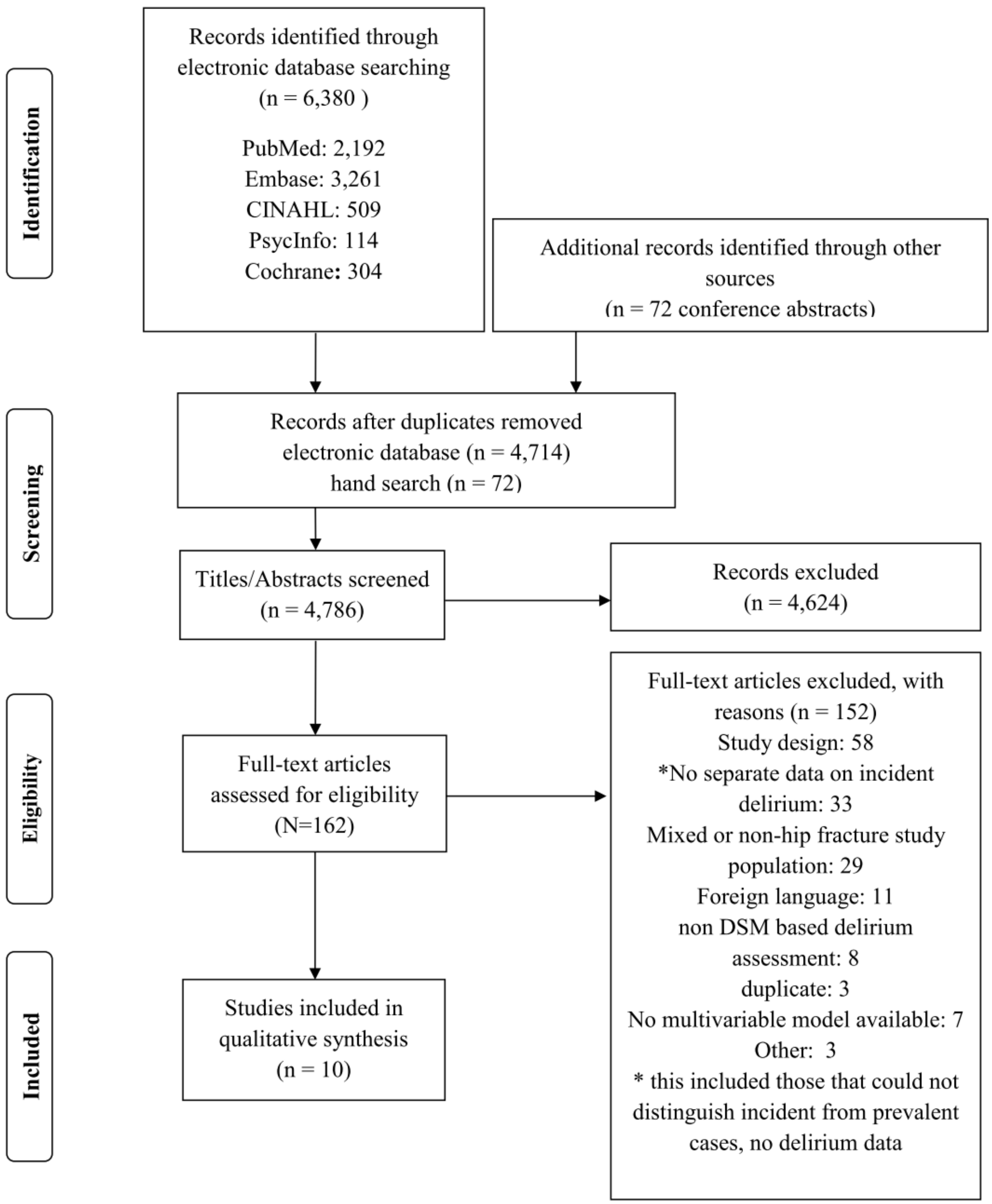

Table II.1. Methods for determining cognitive impairment/dementia

Authors	Testing instruments	DSM [a] criteria	Clinician diagnosis	Medical Records	Committee	Patient interview
Andersson (2001)	OBS [b]					√
Bjoro (2008)	IQ-CODE-SF [c]					√
Goldenberg (2006)	MMSE [d], Set Test [e]	√				√
Juliebo (2009)	IQ-CODE-SF			√	√ (when no proxy information available)	
Lee (2011)	MMSE		√	√		√
Morrison (2003)	4- item screening questionnaire [f]			√		√
Nie (2011)	MMSE [g]					√
Santos (2005)	MMSE					√
Sieber (2011)	MMSE		√	√		√
Zakriya (2002)	MMSE					√

[a] Diagnostic and Statistical Manual (DSM IV) (56); [b] Organic Brain Syndrome (OBS) scale (57); [c] Informant Questionnaire on Cognitive. Decline in the Elderly Short Form (IQ-CODE-SF) (44); [d] Mini-Mental Status Examination (MMSE) (43); [e] Set Test (45); [f] 4-item screen (i. orientation – place and time, ii. circumstances of their fracture – place, time, and circumstances of their fracture, iii. immediate recall of the nature and purpose of the research study, iv. Recall of the name or position of the person administering the informed consent) (46); [g] Different cut-off scores were used to identify cognitive dysfunction depending on educational levels (MMSE <25 for middle school or higher, <21 for elementary school, and <18 for no schooling.). It was noted that 36 % of the patients had attended school or were illiterate.

Table II.2. Baseline characteristics of the selected studies

[a] Age was categorized by those with no delirium or delirium in four studies. Age range was not reported in some of the studies. [b] Diagnostic and Statistical Manual (DSM)-IV; Organic Brain Syndrome (OBS) scale; Confusion Assessment Method (CAM); Memorial Delirium Assessment Scale (MDAS); Delirium Rating Scale-Revised (DRS-R-98). [c] The numbers indicate the proportion (%) of patients with delirium in the entire cohort. The proportion of patients with delirium among cognitively impaired patients are denoted in brackets [ ]. [d] Gender information was not available for the "emergency surgery" subgroup. [e] Median 84, Interquartile range (IQR) 78-88. [f] Age categorized in three groups with number of individuals in each category, but no mean, standard deviation (SD) or age range stated. [g] NR = not reported.

Table II.2. Baseline characteristics of the selected studies

Studies	Country	Setting	Study Period	Sample Size, (% female)	Age Mean (SD) [Range] [a]	Delirium Assessment Tools [b]	Postoperative Assessment Duration	Delirium Incidence in all[c]
Andersson (2001)	Sweden	Central county hospital	02/1994 05/1996	208[d]	no delirium: 78.9 (7.3) [65-95] delirium: 86.0 (6.6) [67-96]	DSM-IV OBS	Daily until delirium resolution	20.2
Bjoro (2008)	Norway	University & community hospital	09/2005 12/2006	204 (77.9)	83 (6.7) [66-100]	CAM MDAS	Daily up to postoperative day 4	34.3 [56.5]
Goldenberg (2006)	USA	Community hospital	11/2000 03/2002	77 (64.9)	81.9 (7.5) [66-98]	CAM	Daily until discharge	48.1
Juliebo (2009)	Norway	University hospital	09/2005 12/2006	187 (77.5)	84 (78-88) [e]	CAM	Daily (weekdays)	36.4 [60.3]
Lee (2011)	USA	University hospital	1999 2008	425 (73.2)	80.2 (6.8) [64-101]	CAM	Daily until discharge	35 [54]
Morrison (2003)	USA	4 city hospitals	07/1997 08/1998	541 (81.7)	age <70 , N= 49 [f] age 70-79, N = 141 age 80+ , N= 351	CAM	Daily (weekdays)	16
Nie (2011)	China	NR [g]	NR	123 (69.1)	no delirium: 75.3 (0.8) delirium: 75 (2)	CAM DRS-R-98	Daily up to 6 days	13
Santos (2005)	Sweden	University hospital	06/2003 07/2003	34 (73.5)	no delirium: 81.5 (10.2) delirium: 82.9 (6.3)	CAM DSM IV	Daily up to 5 days; until discharge if delirium	55.9
Sieber (2011)	USA	University hospital	04/2005 07/2009	236 (71.6)	81.5 (7.1)	CAM	Daily until discharge	25.4
Zakriya (2002)	USA	University hospital	03/1999 12/2000	168 (81.5)	no delirium: 77 (1) delirium: 79 (1)	CAM	Daily until discharge	28

Table II. 3 Analysis of risk factors by significance in bivariate models

Studies by Sieber et al (36) and Zakriya et al. (35) from Table 2 were not included in Table 2 because they are subgroup analysis from the same study cohort as the study by Lee et al. (34). Lee et al. was chosen for this analysis as the study includes the largest number of subjects from the same cohort. P-values are not stated if they were not reported or could not be calculated from other data available.[a] Functional impairment was defined differently in studies: “help from others before admission” (42), ADL score ≥ 2 (39), Barthel index 19 or 20 (47), and FIM score (46). [b] BMI in quartiles (34), BMI ≤ 20kg/m^2 (40, 47), albumin <3.4g/dL (40), albumin (median value) (47), or albumin < 3.5 g/dL (39). [c] American Society of Anesthesiologist (ASA) Physical Status Classification. ASA group III, IV, or V (47), ASA ≥ 4 (34), ASA II, III, or IV (38), ASA I-II or III-V (40), [d] Acute medical conditions included “preoperative medical treatment for cardiovascular or pulmonary problems” (42), “CHF on admission” and “abnormal BP on admission” (46). [e] Polypharmacy was defined as “>5” (40),”≥5” (47), and “>3 medications” (39). [f] BMI (p=0.003), albumin (p=0.26). [g] The goal of this study was to develop a prediction model for the risk of postoperative delirium (POD).These variables were identified as predictors of POD in the bivariate model, but cut off p-value was not reported in the article. [h] BMI (p=0.003), albumin (p=0.64). [i] P-values for the stratified bivariate analysis by dementia status were published by Lee et.al. The p-values presented in this table were calculated by the author for the entire cohort from available data. [j] In this study, p <0.15 in the bivariate analysis was the cut-off value for incorporation into the multivariate model, and thus categorized as “significant.” [k] “abnormal BP” (p=0.12), “abnormal heart rhythm” (p=0.01),”substernal chest pain” (p=0.001), “CHF” (p<0.001), "respiratory compromise" (p=0.59). [1] Nie et al. reported that different cut-off scores were used to identify cognitive dysfunction depending on educational levels (MMSE <25 for middle school or higher, <21 for elementary school, and <18 for no schooling.). However, baseline bivariate statistics are only reported with comparison of group mean MMSE (p=0.61), and not as a dichotomous variable.

Table II.3. Analysis of risk factors by significance in bivariate models

Risk Factors (p-value)	**Cognitive Impair -ment**	**Age**	**Male Gen -der**	**Institu tionaliza -tion**	**Func- tional Impairment [a]**	**BMI and Albumin [b]**	**Multiple Co -morbid- ities**	**ASA [c] Classi -fication**	**Acute Medical Condi -tions [d]**	**Poly- phar- macy [e]**	**Vision Impair- ment**
Studies											
Andersson (2001)	**S** (<0.0001)	**S** (<0.0001)			**S** (<0.002)		**S** (<0.02)		**S** (<0.01)		**S** (<0.0001)
Bjoro (2008)	**S** (0.000)	**S** (0.009)		**S** (0.002)	**S** (0.004)	**S** [f] (0.003) NS (0.26)	NS (0.67)	**S** (0.009)		NS (0.19)	
Goldenberg (2006) [g]	**S**	**S**		**S**	**S**	**S**	**S**			**S**	
Juliebo (2009)	**S** (<0.001)	**S** (0.005)	NS (0.41)	**S** (0.005)	**S** (0.001)	**S** [h] (0.003) NS (0.64)	NS (0.56)	**S** (0.004)		**S** (0.002)	
Lee [i] **(2011)**	**S** (0.000)	**S** (0.002)	**S** (0.004)			NS (0.84)	**S** (0.000)	**S** (0.000)			
Morrison [j] **(2003)**	**S** (<0.001)	**S** (0.02)	**S** (0.11)	**S** (0.08)	**S** (0.001)				**S** [k]		
Nie (2011)	NS [l] (0.61)	NS (0.54)	NS (0.39)								
Santos (2005)	**S** (0.03)	NS (0.62)	NS (0.36)	**S** (0.013)				NS (0.34)			

II4. Analysis of risk factors by significance in multivariable models.

P-values and effect sizes are not stated if they were not reported or could not be calculated from other data available. Hazard Ratio (HR), Odds Ratio (OR), Relative Risk (RR). [a] (BMI $\leq$ 20kg/m^2) (40, 47) or albumin < 3.5 (39). [b] Lee et al did not put ASA Physical Status Classification in the multivariate model even though they were significant in the bivariate model due to collinearity with other variables (34). [c] Acute medical conditions included "preoperative medical treatment for cardiovascular or pulmonary problems" (42), "CHF on admission" and "abnormal BP on admission" (46). [d] ASA Physical Status Classification or "severity of illness" was treated as a "precipitating factor" in this analysis and was incorporated into multivariate analysis with other precipitating factors. [e] P-values were calculated from OR with 95% CI reported in the article. [f] Set Test (ST) cut off score <20 (p=0.06), MMSE <24 (p=0.03). [g] Age is noted as one of the independent predictors of POD in multivariate logistic regression analysis with OR of 5.1 (95% CI 0.9-26.8). Calculated p-value is 0.0598 or 0.06. Therefore, it was categorized as not significant (NS) in this systematic review. [h] In this study, the highest RR was 5.4 for parenteral morphine sulfate equivalent of < 10 mg per day. [i] "abnormal BP" (RR 2.3; p=0.01), "abnormal heart rhythm" (RR 1.7; p=0.3),"substernal chest pain" (RR1.9; p=0.4), "CHF" (RR 2.9; p<0.001), [j] Nie et al. did not report a p-value, but reported OR 3.88 (95% CI 0.45-33.19) which calculates to p-value of 0.28.

Table II.4. Analysis of risk factors by significance in multivariate models

Risk Factors (p-value)	Cognitive Impair-ment	Age	Gen-der	Institu-tionaliza-tion	Functional Impairment [a]	BMI and Albumin [b]	Multiple Co-morbidities	ASA [c] Classi-fication	Acute Medical Condi-tions [d]	Poly-pharmacy [e]	Vision Impair-ment
Studies											
Andersson (2001)	**S** (<0.009) HR 1.30	**S** (<0.003) HR 1.09	NS		NS		**S** (<0.0001) HR 12.24		**S** (<0.01) HR 2.84		**S** (<0.0009) HR 3.92
Bjoro (2008)	**S** (0.001) OR 3.90	NS (0.10) OR 1.9		NS (0.19) OR 2.1	NS (0.55) OR 0.8	**S** (0.01) OR 2.3		NS (0.06) [d] OR 1.8			
Goldenberg (2006) [e]	**S** [f] (0.006) OR 13.1 (0.03) OR 6.9	NS [g] (0.06) OR 5.1		NS	NS	**S** (0.03) OR 1.8	NS			**S** (0.02) OR 33.6	
Juliebo (2009)	**S** (0.005) OR 2.93	NS		NS	NS	**S** (0.01) OR 2.92		NS		NS	
Lee (2011)	**S** (<0.001) OR 2.74	**S** (0.004) OR 1.05	**S** (0.003) OR 2.10				**S** (0.005) OR 1.14				
Morrison (2003) [h]	**S** (<0.001) RR 3.6	NS (0.8) RR1.0	NS (0.08) RR 0.6	NS (0.5) RR1.3	NS (0.98) RR 1.0				**S** [i]		
Nie (2011)	NS [j] (0.28) OR 3.88										
Santos (2005)	NS (0.32) OR 1.21		NS (0.37) OR 1.17	NS (0.17) OR 1.30							

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CHAPTER III

RISK PREDICTION MODEL OF POSTOPERATIVE DELIRIUM IN HIP FRACTURE POPULATION

METHODS

Derivation Cohort

Entire Group

The derivation cohort was derived from a study which comprised of 726 consecutive hip fracture repair patients above age 65 who were approached for consent to collect their peri-operative clinical data for research purpose from 1999 and 2008 at the Johns Hopkins Bayview Medical Center. Patients who were determined to have preoperative delirium by a trained research nurse based on the Confusion Assessment Method (CAM) (58) were ineligible for the study. Of the remaining eligible patients, 429 individuals with complete postoperative delirium data were included in the analysis. Postoperative delirium was measured by CAM on the second postoperative day (POD2). Confusion Assessment Method (CAM) consists of two core features 1) acute onset and fluctuating course 2) inattention, and two other supporting features 3) disorganized thinking and 4) altered level of consciousness. The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4 (58). The study was approved by the Johns Hopkins Institutional Review Board, and all participants gave informed consent.

Non-demented group

The derivation cohort was also stratified by cognitive status, and a separate cohort of 287 individuals who did not meet the criteria for probable dementia diagnosis was established. This cohort will be hitherto referred as the “non-demented” group.

Validation cohort

The validation cohort was derived from a study which comprised of 83 consecutive hip fracture repair patients who were enrolled in the study A Strategy to Reduce the Incidence of Post-operative Delirium in Elderly patients (STRIDE). This study was started at the Johns Hopkins Bayview Medical Center in November 2011 and is still on-going at this time. STRIDE is a randomized controlled trial of light versus heavy intraoperative sedation (anesthesia) in individuals with hip fracture. Exclusion criteria include preoperative delirium at the time of screening, refusal or inability to have spinal anesthesia, or MMSE less than 15. Delirium assessments are completed by trained research assistants who administers MMSE (43), CAM, Digit Span, and Delirium Rating Scale-Revised-98 (DRS-R-98) (41) preoperatively, and then daily from postoperative day (POD) 1 to POD 5 or up to the time of hospital discharge. They also interview the patient, family, nurse and review medical records including physician notes. Consensus Diagnostic Committee (CDC) consisting of two psychiatrists and one geriatrician arrive at a consensus diagnosis of delirium based on the data collected by the research assistants. For this study, a patient was classified to have postoperative delirium if he or she had CDC adjudicated delirium diagnosis at any time during the hospitalization. The methods for determining delirium for the derivation and validation cohort are summarized in Table III.1.

Preoperative risk factors for building prediction model were chosen based on previous data analyses involving this study population and from the literature including systematic reviews (16, 18, 59, 60). Preoperative Risk factors were categorized into demographics including age, gender, race, current smoking status, current alcohol use, body mass index (BMI); neurological and psychiatric including history of probable dementia, cerebrovascular accident (CVA)/transient ischemic attack (TIA)/carotid endarterectomy (CEA) diagnosis, Parkinson's disease, depression, and psychiatric disorder other than depression; medical comorbidities including number of comorbidities, coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation, hypertension (HTN), diabetes (DM), chronic renal insufficiency (CRI), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), cancer, hypothyroidism, syncope, and American Society of Anesthesiologists (ASA) Physical Classification. Probable dementia diagnosis was assigned if either the patient had a MMSE score of less than 24 (43) or was given a diagnosis of dementia by a geriatrician during pre-operative evaluation. MMSE cut-off score was used to capture patients with possible underlying dementia who may not have been recognized on outpatient basis (59).

Analyses

Preoperative factors were compared between individuals who experienced postoperative delirium and those who did not using t-test for continuous variables and χ^2

test for dichotomous or categorical variables. The selected variables were examined for their missingness. All of the chosen variables had less than 10 % of missing values except two variables height and albumin level, which had missing variables of 15.9 % and 16.1 % respectively. Since BMI (derived from height and weight) and albumin level were determined to be important risk factors for postoperative delirium in hip fracture population (60), these variables were also included in the model after two fold multiple imputation was performed using Imputation by Chained Equations (ICE). BMI variable was created after the multiple imputation of height and weight variables. We also conducted sensitivity analysis based on missingness of the variables BMI and albumin prior to multiple imputation, and the incidence of delirium was not statistically different between those who were missing these variables compared to those who were not.

Variables that were identified as independent risk factors ($p \leq 0.10$) of postoperative delirium in the bivariate analysis were chosen for backward step-wise multivariable selection, which is considered to be superior to forward selection (61). Collinearity among all of the chosen variables was examined by testing variance inflation factors (VIF) both in the original and the imputed dataset. In addition, further examination of potential collinearity among variables which may reflect frailty/inflammatory state including BMI, albumin level and Parkinson's disease (62, 63) were performed separately in the original and imputed dataset. Following the events per variable (EPV) rule with 10 events allowed per variable, (64, 65) it was determined that the model allowed up to 14 variables (147/429 subjects with postoperative delirium).

If a risk factor was available in different types of variable, an effort was made to choose continuous variable over dichotomous or categorical variable. Some variables that were available as both continuous and categorical variables were separately tested in multivariable models to determine which had the best fit in the model. Age was tested as a continuous or a categorical (decades) variable, and the American Society of Anesthesiologists (ASA) Physical Status Classification System was tested as a categorical (1 to 4) or a dichotomous (ASA < 4 or ASA ≥ 4) variable (66). Number of comorbidities were tested as a continuous or a dichotomous variable based on the median number of comorbidities (5) in the cohort (≤ 5 or >5). BMI was tested as a continuous or a categorical variable (underweight BMI < 18.5, normal $18.5 \leq$ BMI < 25, overweight $25 \leq$ BMI <30, obese BMI ≥ 30 in/ft^2). Albumin was also tested as a continuous variable, two dichotomous variables with different cut off values (albumin < 3.5 or ≥ 3.5 mg/dL) or (albumin < 3.4 or ≥ 5.0 mg/dL). The former cut off value was based on the literature (39) and the latter based on the study institution's reference range. Other laboratory values including hemoglobin, blood urea nitrogen (BUN)/creatinine ratio, and white blood cell (WBC) counts were dichotomized by the reference range set by the study institution. As the interaction between age and gender was found to be one of the important preoperative risk factors of postoperative delirium in this study population (in press, Oh, et al., the Journal of the American Geriatrics Society), age-gender interaction term was also tested in the model.

Receiver operating characteristic (ROC) was used as the primary statistic of model performance, and internal validation was performed with bootstrap resampling procedure (67). Averages of bootstrap performance was derived from 1,000 repetitions, and estimated performance was derived by correcting for optimism (68). In order to determine whether the model is a good fit for the data, Hosmer-Lemeshow goodness-of-fit test was performed. (69)

External validation was performed on hip fracture population at the same institution (Johns Hopkins Bayview Medical Center) from a different time period (temporal validation). Although there were five subjects with dementia diagnosis, MMSE < 24 was used as a surrogate for "probable dementia" diagnosis in order to be more congruent with the derivation cohort. All statistical analyses were performed using STATA (College Station, TX: StataCorp LP).

RESULTS

The overall incidence of postoperative delirium in the derivation population was 34 % (147/429). At baseline, mean age of the study population was 81 (SD 6.9). They were more likely to be female and predominantly white. Roughly a third (33 %) of the patients met the predefined criteria for probable dementia. Among the medical co-morbidities, hypertension (HTN) was the most common comorbidity, followed by coronary artery disease (CAD) and diabetes. Most patients were in the ASA Physical Classification 3, which is designated for patients with severe systematic disease (70). In terms of laboratory values, none of the preoperative risk factors examined including anemia, azotemia, leukocytosis or low albumin levels differed by postoperative delirium status (Table III.2). The baseline characteristics were similar in the non-demented subgroup, with exception of history of PD, which was no longer statistically significant at baseline (Table III.3)

In bivariate analysis of the derivation set, individuals who were older or male gender had higher risk of delirium. Probable dementia or Parkinson's disease (PD) was also associated with higher risk of delirium, and there was a trend towards significance with history of CVA/TIA/CEA. Among co-morbidities, history of CHF or atrial fibrillation was associated with higher risk of delirium as were number of comorbidities and higher level of the ASA Physical Classifications System (Table III.4). In the non-demented group, the bivariate associations remained similar except for BMI, history of psychiatric disorder other than depression, and history of peripheral vascular disease (PVD) which were significantly associated in the non-demented group, and PD which was not significant.

There were total of 147 postoperative delirium episodes, which allowed selection of up to 14-15 variables for our prediction model (64, 65). There were 10 variables that were chosen for modeling building, including 8 variables that were chosen based on having the cut-off of $p \leq 0.10$ in bivariate analysis (age, gender, probable dementia, Parkinson's disease, CHF, atrial fibrillation, number of comorbidities, and ASA) (Table III.4) and 2 variables that were chosen from the systematic review (BMI and albumin) (60). Using cut-off of $p \leq 0.1$, step-wise regression was performed by backward elimination. The following 6 variables remained in the model including age (continuous), gender (dichotomous), probable dementia (dichotomous), Parkinson's disease (dichotomous), ASA (categorical) and albumin (continuous) (Table III.6). CHF, atrial fibrillation, number of comorbidities, and BMI were eliminated.

In the non-demented subgroup, there were 72 postoperative delirium episodes. There were 10 variables that were chosen for model building, including 9 variables that were chosen based on having the cut-off of $p \leq 0.1$ in bivariate analysis (age, gender, BMI, history of psychiatric disorder other than depression, CHF, atrial fibrillation, PVD, number of comorbidities, and ASA) (Table III.5) and 1 variable that was chosen from the systematic review (albumin).Using cut-off of $p \leq 0.1$, step-wise regression was performed by backward elimination. The following 5 variables remained in the model including age (continuous), gender (dichotomous), history of psychiatric disorder other than depression (dichotomous), PVD (dichotomous), and ASA (categorical) (Table III.7). CHF, atrial fibrillation, number of comorbidities, BMI and albumin were eliminated.

Internal validation using bootstrap technique with 1000 repetitions was performed with the model including only independent predictors. The receiver operating characteristic (ROC) was 0.73 (Figure III.1) optimism was 0.01, with resulting optimism corrected ROC of 0.72. Hosmer-Lemeshow goodness-of-fit test showed that the probability that a χ^2 statistic exceeds 12.49 was $p = 0.13$ (Figure III.2), therefore this test did not provide evidence to reject the model. External validation with the validation cohort resulted in ROC of 0.63 (Figure III.3). Hosmer-Lemeshow goodness-of-fit test showed that the probability that a χ^2 statistic exceeds 14.83 was $p = 0.06$ (Figure III.4).

When the interaction variable of age and gender was incorporated into the analysis, it resulted in a model with 9 variables including age, gender, age*gender (interaction), probable dementia, Parkinson’s disease, number of comorbidities, ASA, and albumin. Although incorporation of an interaction variable of age and gender resulted in a prediction model with superior discrimination (ROC 0.75), the external validation was inferior (ROC 0.57).

In the non-demented subgroup, the internal validation using bootstrap technique with 1000 repetitions resulted in ROC of 0.70 and optimism of 0.03, with resulting optimism corrected ROC of 0.67. External validation was not completed as history of psychiatric disorder other than depression was not collected as part of the validation cohort.

DISCUSSION

In this study, we developed a new preoperative risk prediction model (RPM) of postoperative delirium in hip fracture population. We identified 6 preoperative risk factors including age, gender, dementia, Parkinson's disease, ASA Physical Status Classification, and albumin level, and developed a RPM which performed moderately well in internal validation (ROC = 0.72). However, the model performed less than optimally in the external validation.

The innovation of our model is that this RPM was developed based on risk factors identified from a hip fracture population, as compared to a previous model which was developed with risk factors identified from a general medical population and applied to a hip fracture population (17). The strengths of this RPM include selection of risk factors based on prior studies in this population including a systematic review which specifically examined preoperative risk factors of postoperative delirium in hip fracture population (60), which is considered to be of great importance (71). We also applied multiple imputation to minimize missing data in variables that were identified as important in the systematic review. Finally, bootstrapping technique for internal validation was used, which provides stable estimates with low bias compared to split-sample analyses or cross-validation methods (68).

One of the reasons for less than optimal external validation result of our prediction model may be due to the issues of methodological transportability. Differences in the methods used to define variables and collect data can result in problems with methodological transportability in external validation (72). One of the most important differences between the derivation cohort and validation cohort in our study is ascertainment of postoperative delirium as noted in Table III.1. In the derivation cohort, postoperative delirium assessments were done on postoperative day 2, whereas in the validation cohort, they were completed from postoperative day 1 to day 5 or up to the day of discharge. In addition, delirium outcome in the derivation cohort was based on the CAM, but in the validation cohort, delirium outcome was based on the adjudication from the Consensus Diagnosis Committee (CDC). The CDC considered more comprehensive information including the CAM, DRS-R-98, MMSE, history from informants and medical records. Another difference is ascertainment of probable dementia. In the derivation cohort, dementia variable was a combined variable of either having MMSE less than 24 or having preoperative diagnosis of dementia by a physician. In the validation cohort, dementia variable was based on MMSE less than 24 only, as baseline data of dementia diagnosis is not complete at this time. Finally, the external validation was performed in a small subset of a cohort, due to the nature of the on-going study.

Another reason for the poor external validation results may be that even though the underlying cognitive impairment/dementia is an important risk factor, the validation cohort consists of relatively cognitively intact cohort. This may be due to the fact that one of the exclusion criteria is MMSE <15, whereas there was no MMSE exclusion criteria in the derivation cohort. Although an attempt was made to develop a separate RPM model based on "non-demented" individuals from the derivation cohort, it was less than optimal as it was built on a smaller group of individuals and due to some of the significant variables missing in the validation cohort.

There are also other variables such as preoperative functional status and frailty which are thought to be important preoperative risk factors for postoperative delirium, but were not incorporated in the current model because these variables were not consistently collected in the data set of the derivation cohort. BMI was found to be significant in two of the studies selected for a systematic review of risk factors for postoperative delirium in hip fracture population (60). However, it did not come up as a significant variable in step-wise regression performed by backward elimination even though different models were tested with BMI both as a continuous and as a categorical variable. In addition, when different bootstrap models with and without BMI were compared, the more parsimonious model without BMI performed slightly better in terms of discrimination.

One of the most important findings that we can learn from this study is that preoperative risk factors alone cannot explain all the risks for postoperative delirium in hip fracture population. There are also intraoperative and postoperative factors that are important risk factors for development of postoperative delirium that are difficult to know prior to surgery. However, preoperative RPM may be useful in stratifying patients for interventions to prevent delirium by enriching the target population. In addition, there may be biomarkers that may be developed in the future that can strengthen the discrimination power of the preoperative RPM for postoperative delirium. Future directions include temporal validation on full dataset once the STRIDE population of 200 subjects becomes available. In addition, a full external validation on a hip fracture population in another center would be informative regarding the utility of our developed model.

Table III.1. Methods for determining delirium: comparison between derivation and validation cohorts

Cohorts	Testing instruments	Medical Records	Patient interview	Committee	Evaluation duration
Derivation cohort	CAM [a]		√		POD [b] 2
Validation cohort	CAM Digit Span DRS-R-98 [c] MMSE [d]	√	√	√	POD1-5 or discharge

[a] Confusion Assessment Method (CAM) (58); [b] Postoperative day (POD); [c] Delirium Rating Scale-Revised (DRS-R-98)(41); [d] Mini-Mental Status Examination (MMSE) (43).

Table III.2. Baseline data of patients with hip fracture repair by delirium status: demographic and preoperative characteristics

[a] Body Mass Index (BMI) (N = 356, 17 % missing value). Percentages were calculated based on total N = 356, N = 239 in “No delirium” group and N = 117 in “Delirium” group; [b] Clinical history of previous stroke or transient ischemic attacks or carotid endarterectomy; [c] Psychiatric disorders other than depression; [d] Coronary Artery Disease - clinical history of previous myocardial infarction or angina or coronary revascularization (angioplasty, CABG); [e] Congestive Heart Failure - documentation of prior hospital admission with congestive heart failure or ejection fraction < 40 %; ; [f] Peripheral Vascular Disease – history or surgical procedure performed for PVD, claudication, inter-arm asymmetry in blood pressure; [g] Chronic Renal Insufficiency – serum creatinine > 1.5 mg/dl in males or > 1.3 mg/dl in females ; [h] Number of comorbidities; [i] ASA - American Society of Anesthesiologist Physical Status Classification System (1. A normal healthy patient; 2. A patient with mild systemic disease; 3. A patient with severe systemic disease; 4. A patient with severe systemic disease that is a constant threat to life (70) (N = 418, 2.6 % missing value). Percentages were calculated based on total N = 418, N = 275 in “No delirium” group and N = 143 in “Delirium” group;[j] Anemia - Male hematocrit <41, Female hematocrit <36. [k] Azotemia - BUN/creatinine ratio >20; [l] Leukocytosis ->11,000 WBC in the initial CBC; [m] Albumin as a continuous variable – mean 3.98 mg/dL (SD 0.52). There was no statistically significant difference between those without delirium compared to those with delirium 3.96 (SD 0.55) vs.4.03 (SD 0.43), p = 0.90.

Table III.2. Baseline data of patients with hip fracture repair by delirium status: demographic and preoperative characteristics

Risk Factors	Total (N = 429)	No Delirium (N = 282)	Delirium (N = 147)	P-value
Demographics & BMI				
Age-years, mean ± (SD)	81 (6.9)	80 (6.9)	82 (6.8)	**0.002**
Gender, male (%)	115 (26.8)	63 (22.3)	52 (35.4)	**0.004**
Race, non-white, n (%)	19 (4.4)	12 (4.3)	7 (7.4)	0.89
Current smoking, n (%)	67 (15.6)	46 (16.3)	21 (14.3)	0.53
Current alcohol use, n (%)	51 (11.9)	34 (12.1)	17 (11.6)	0.83
Body mass index [a]				
<18.5 (underweight), n (%)	48 (13.5)	30 (12.6)	18 (15.4)	0.61
18.5-24.9 (normal), n (%)	167 (46.9)	109 (45.6)	58 (49.6)	
25.0-29.9 (overweight), n (%)	103 (28.9)	72 (30.1)	31 (26.5)	
≥30.0 (obese), n (%)	38 (10.7)	28 (11.7)	10 (8.5)	
Neurological & Psychiatric				
Dementia, n (%)	142 (33.1)	67 (23.8)	75 (51)	**<0.001**
CVA/TIA/CEA [b], n (%)	83 (19.3)	47 (16.7)	36 (24.5)	**0.05**
Depression, n (%)	69 (16.1)	43 (15.2)	26 (17.7)	0.51
Psychiatric disorder [c], n (%)	41 (9.6)	23 (8.2)	18 (12.2)	0.18
Parkinson's disease, n (%)	13 (3.0)	5 (1.8)	8 (5.4)	**0.04**
Medical				
Hypertension, n (%)	312 (72.0)	206 (73.05)	106 (72.11)	0.79
CAD [d], n (%)	124 (28.9)	82 (29.08)	42 (28.57)	0.90
Diabetes, n (%)	101 (23.5)	72 (25.5)	29 (19.7)	0.18
COPD, n (%)	92 (21.4)	62 (22.0)	30 (20.4)	0.69
CHF [e], n (%)	85 (19.8)	48 (17.0)	37 (25.2)	**0.05**
Atrial fibrillation, n (%)	82 (19.1)	46 (16.3)	36 (24.5)	**0.04**
Cancer, n (%)	65 (15.2)	43 (52.4)	22 (15.0)	0.93
Hypothyroidism, n (%)	63 (14.7)	43 (15.2)	20 (13.6)	0.64
PVD [f], n (%)	52 (12.1)	30 (10.6)	22 (15.0)	0.20
CRI [g], n (%)	48 (11.2)	31 (11.0)	17 (11.6)	0.88
Syncope, n (%)	22 (5.1)	11 (3.9)	11 (7.5)	0.11
#Comorbidities [h], mean ± (SD)	4.8 (2.4)	4.5 (2.3)	5.5 (2.6)	**<0.001**
ASA 2 [i], n (%)	72 (17.2)	63 (22.9)	9 (6.3)	**<0.001**
ASA 3	290 (69.4)	184 (66.9)	106 (74.1)	
ASA 4	56 (13.4)	28 (10.2)	28 (19.6)	
Laboratory				
Anemia [j], n (%)	233 (54.3)	154 (54.6)	79 (53.7)	0.86
Azotemia [k], n (%)	220 (51.3)	143 (50.7)	77 (52.4)	0.72
Leukocytosis [l], n (%)	139 (32.4)	93 (33.0)	46 (31.3)	0.54
Low albumin [m], n (%)	47 (11.0)	36 (12.8)	11 (7.5)	0.15

Table III.3. Baseline data of patients with hip fracture repair by delirium status: demographic and preoperative characteristics among the non-demented group

[a] Body Mass Index (BMI) (N = 252, 12 % missing value). Percentages were calculated based on total N = 252, N = 190 in "No delirium" group and N = 62 in "Delirium" group

Table III.3. Baseline data of patients with hip fracture repair by delirium status: demographic and preoperative characteristics among the non-demented group

Risk Factors	Total (N = 287)	No Delirium (N = 215)	Delirium (N = 72)	P-value
Demographics & BMI				
Age-years, mean ± (SD)	80 (7.0)	79 (6.9)	81 (7.0)	**0.02**
Gender, male (%)	78 (27.8)	50 (23.3)	28 (38.9)	**0.01**
Race, non-white, n (%)	10 (3.5)	7 (3.3)	3 (2.0)	0.72
Current smoking, n (%)	46 (16.0)	38 (17.7)	8 (11.1)	0.18
Current alcohol use, n (%)	35 (12.3)	29 (13.6)	6 (8.5)	0.25
Body mass index [a]				
<18.5 (underweight), n (%)	31 (12.3)	21 (11.0)	10 (16.1)	0.19
18.5-24.9 (normal), n (%)	113 (44.8)	82 (43.2)	31 (50.0)	
25.0-29.9 (overweight), n (%)	79 (31.4)	61 (32.1)	18 (29.0)	
≥30.0 (obese), n (%)	29 (11.5)	26 (13.7)	3 (4.8)	
Neurological & Psychiatric				
CVA/TIA/CEA, n (%)	46 (16.0)	31 (14.4)	15 (20.8)	0.20
Depression, n (%)	40 (13.9)	29 (13.5)	11 (15.3)	0.68
Psychiatric disorder, n (%)	30 (10.5)	18 (8.4)	12 (16.7)	**0.05**
Parkinson's disease, n (%)	8 (2.8)	4 (1.9)	4 (5.6)	0.10
Medical				
Hypertension, n (%)	208 (72.5)	156 (72.6)	52 (72.2)	0.91
CAD, n (%)	86 (29.0)	67 (31.2)	19 (26.4)	0.43
Diabetes, n (%)	67 (23.3)	53 (24.7)	14 (19.4)	0.36
COPD, n (%)	61 (21.3)	46 (21.4)	15 (20.8)	0.91
CHF, n (%)	57 (19.9)	36 (16.7)	21 (29.2)	**0.02**
Atrial fibrillation, n (%)	51 (17.8)	31 (14.4)	20 (27.8)	**0.01**
Cancer, n (%)	40 (13.9)	33 (15.4)	7 (9.7)	0.23
Hypothyroidism, n (%)	36 (12.5)	29 (13.5)	7 (9.7)	0.40
PVD, n (%)	34 (11.8)	30 (14.0)	22 (30.6)	**0.01**
CRI, n (%)	26 (9.1)	21 (9.8)	5 (6.9)	0.46
Syncope, n (%)	14 (4.9)	9 (4.2)	5 (6.9)	0.35
#Comorbidities, mean ± (SD)	4.5 (2.4)	4.3 (2.2)	5.1 (2.7)	**0.01**
ASA 2, n (%)	60 (20.9)	54 (25.1)	6 (8.3)	**0.003**
ASA 3	195 (67.9)	142 (66.0)	53 (73.6)	
ASA 4	32 (11.1)	19 (8.8)	13 (18.1)	
Laboratory				
Anemia, n (%)	147 (51.2)	111 (51.6)	36 (50.0)	0.81
Azotemia, n (%)	137 (47.7)	104 (48.4)	33 (45.8)	0.73
Leukocytosis, n (%)	88 (30.1)	70 (32.6)	18 (25.0)	0.27
Low albumin, n (%)	30 (10.5)	24 (11.2)	6 (8.3)	0.65

Table III.4. Bivariate analysis of preoperative risk factors for postoperative delirium

Risk Factors	Total (N=429) Odds Ratio (95% CI)	p-value
Demographics & BMI		
Age-years	1.05 (1.02, 1.08)	**0.002**
Gender (male)	1.90 (1.23, 2.95)	**0.004**
Race	1.15 (0.51, 2.63)	0.74
Current Smoking	0.84 (0.48, 1.47)	0.53
Current Alcohol use	0.93 (0.50, 1.74)	0.83
Body mass index	0.83 (0.64, 1.09)	0.18
Neurological & Psychiatric		
Dementia	3.34 (2.19, 5.11)	**<0.001**
CVA/TIA/CEA	1.61 (0.99, 2.63)	0.06
Depression diagnosis	1.20 (0.71, 2.05)	0.51
Psychiatric disorder	1.56 (0.81, 2.99)	0.18
Parkinson’s disease	3.18 (1.02, 9.89)	**0.05**
Medical		
Hypertension	0.94 (0.60, 1.47)	0.79
CAD	0.97 (0.62, 1.51)	0.90
Diabetes	0.72 (0.44, 1.17)	0.19
COPD	0.91 (0.55, 1.48)	0.69
CHF	1.63 (1.01, 2.65)	**0.05**
Atrial fibrillation	1.66 (1.01, 2.71)	**0.04**
Cancer	0.97 (0.56, 1.70)	0.93
Hypothyroidism	0.87 (0.49, 1.55)	0.64
PVD	1.47 (0.82, 2.66)	0.20
CRI	1.05 (0.56, 1.96)	0.88
Syncope	1.98 (0.84, 4.70)	0.12
# Comorbidities	1.17 (1.08, 1.28)	**<0.001**
ASA	2.47 (1.66, 3.69)	**<0.001**
Laboratory		
Anemia	0.97 (0.65, 1.44)	0.86
Azotemia	1.08 (0.72, 1.61)	0.72
Leukocytosis	0.87 (0.56, 1.35)	0.54
Albumin	1.34 (0.85, 2.11)	0.21

Table III.5. Bivariate analysis of preoperative risk factors for postoperative delirium in the non-demented group

Risk Factors	Total (N=287) Odds Ratio (95% CI)	p-value
Demographics & BMI		
Age-years	1.05 (1.00, 1.09)	**0.03**
Gender	2.10 (1.19, 3.71)	**0.01**
Race	1.36 (0.48, 3.90)	0.57
Current Smoking	0.58 (0.25, 1.30)	0.18
Current Alcohol use	0.59 (0.23, 1.47)	0.26
Body mass index	0.69 (0.48, 0.98)	**0.04**
Neurological & Psychiatric		
CVA/TIA/CEA	1.56 (0.79, 3.10)	0.20
Depression diagnosis	1.17 (0.55, 2.48)	0.68
Psychiatric disorder	2.17 (0.99, 4.75)	**0.05**[a]
Parkinson's disease	3.10 (0.76, 12.74)	0.12
Medical		
Hypertension	0.97 (0.53, 1.76)	0.91
CAD	0.79 (0.43, 1.43)	0.43
Diabetes	0.73 (0.38, 1.42)	0.36
COPD	0.96 (0.50, 1.85)	0.91
CHF	2.05 (1.10, 3.81)	**0.02**
Atrial fibrillation	2.28 (1.20, 4.33)	**0.01**
Cancer	0.59 (0.25, 1.40)	0.23
Hypothyroidism	0.69 (0.29, 1.64)	0.40
PVD	2.70 (1.29, 5.65)	**0.008**
CRI	0.69 (0.25, 1.89)	0.47
Syncope	1.70 (0.55, 5.25)	0.36
# Comorbidities	1.15 (1.03, 1.29)	**0.01**
ASA	2.41 (1.44, 4.03)	**0.001**
Laboratory		
Anemia	0.94 (0.55, 1.60)	0.81
Azotemia	0.91 (0.53, 1.56)	0.73
Leukocytosis	0.71 (0.38, 1.32)	0.27
Albumin	1.24 (0.48, 3.21)	0.65

[a] p-value = 0.054

Table III.6. Multivariable analysis of preoperative risk factors for postoperative delirium

Risk Factors	Odds Ratio (95% CI)	p-value
Age	1.04 (1.00, 1.07)	**0.03**
Gender (male)	2.28 (1.40, 3.73)	**0.001**
Dementia	2.91 (1.85, 4.57)	**<0.001**
Parkinson's disease	4.34 (1.16, 16.26)	**0.03**
ASA	2.02 (1.32, 3.08)	**0.001**
Albumin (mg/dL)	1.63 (1.03, 2.59)	**0.04**

*Logistic regression based on multiply imputed (x1) dataset

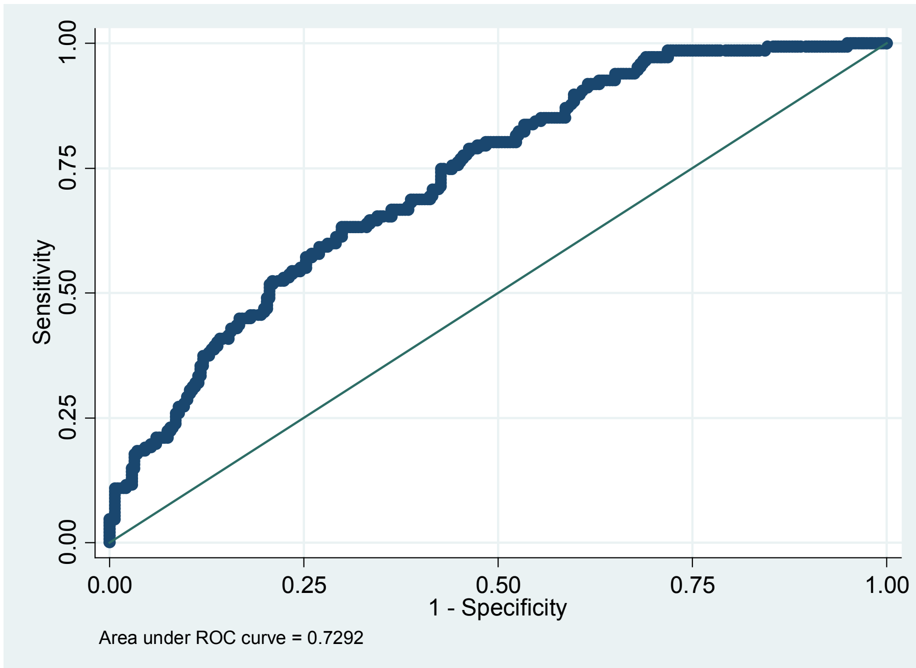
Table III.7. Multivariable analysis of preoperative risk factors for postoperative delirium in the non-demented group

Risk Factors	Odds Ratio (95% CI)	p-value
Age	1.05 (1.01, 1.10)	**0.02**
Gender (male)	2.31 (1.24, 4.30)	**0.01**
Psychiatric disorder[a]	2.46 (1.05, 5.75)	**0.04**
PVD[b]	2.37 (1.08, 5.23)	**0.03**
ASA	1.90 (1.09, 3.29)	**0.02**

*Logistic regression based on multiply imputed (x1) dataset

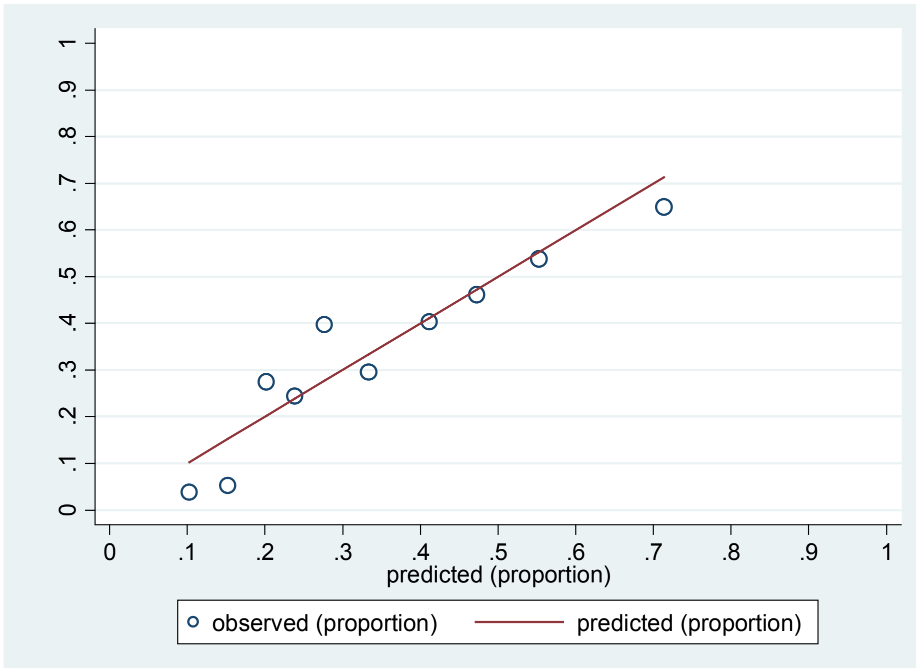
[a] History of psychiatric disorder other than depression; [b] History of peripheral vascular disease (PVD)

Figure III.1 Receiver operating characteristic (ROC) of internal validation for prediction model of postoperative delirium.



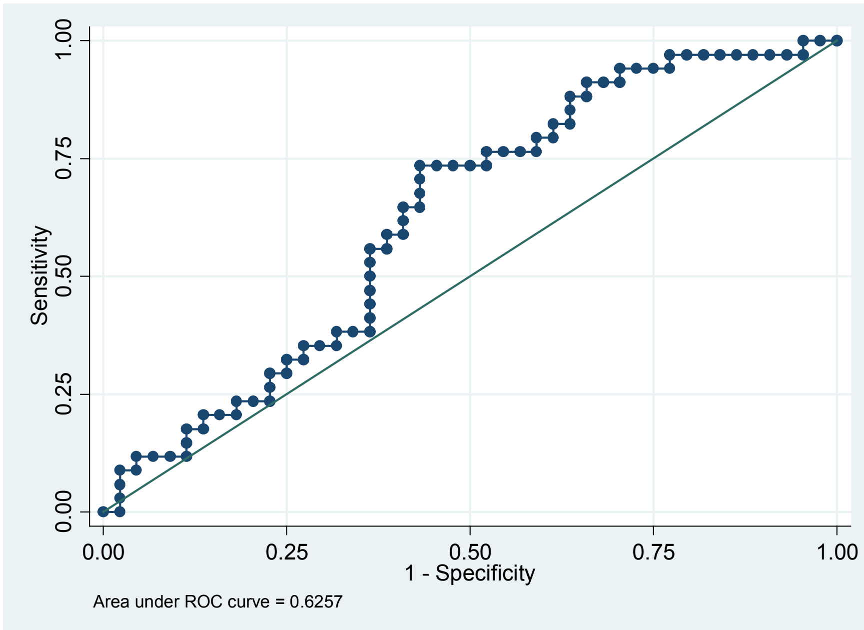
Internal validation using bootstrap technique with 1000 repetition and adjusted for optimism of 0.01, resulted in optimism corrected ROC of 0.72.

Figure III.2 Calibration of prediction model for postoperative delirium in internal validation.



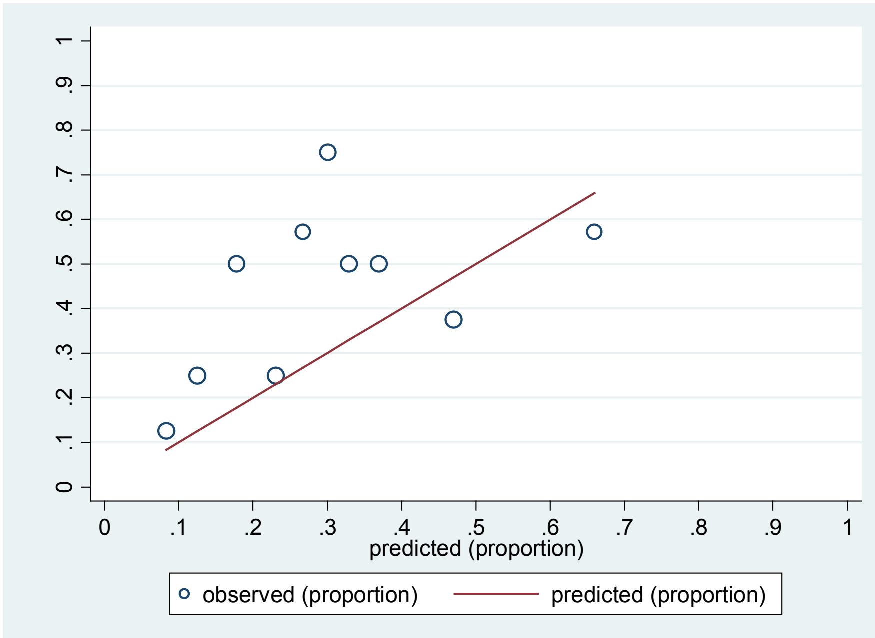
Hosmer-Lemeshow goodness-of-fit test showed that the probability that a χ^2 statistic exceeds 12.49 was p = 0.13 (Figure 2), therefore this test did not provide evidence to reject the model.

Figure III.3 Receiver operating characteristic (ROC) of external validation for prediction model of postoperative delirium.



External validation with the validation cohort resulted in ROC of 0.63

Figure III.4 Calibration of prediction model for postoperative delirium in external validation.



Hosmer-Lemeshow goodness-of-fit test showed that the probability that a χ^2 statistic exceeds 14.83 was p = 0.06

CHAPTER IV

CSF BIOMARKERS OF POSTOPERATIVE DELIRIUM IN HIP FRACTURE POPULATION

METHODS

The study is comprised of 83 consecutive hip fracture repair patients who were enrolled in the study A Strategy to Reduce the Incidence of Post-operative Delirium in Elderly patients (STRIDE). This study was started at the Johns Hopkins Bayview Medical Center in November 2011 and is still on-going at this time. STRIDE is a randomized controlled trial of light versus heavy intraoperative sedation (anesthesia) in individuals with hip fracture.

<u>Inclusion/Exclusion Criteria</u>

Inclusion Criteria

(a) Patient is able to read, write, speak and understand English, and Mini-Mental State Examination (MMSE) (43) score ≥ 15 (max=30).

Exclusion Criteria

(a) Patient does not meet guidelines to receive spinal anesthesia, (b) patient refusal to give informed consent, (c) patient is younger than 65 years of age at admission, (d) patient is unable to read/write/speak/understand English, (e) MMSE < 15, (f) patient has preoperative delirium, (g) patient is intubated, (h) patient has severe chronic obstructive pulmonary disease (COPD) based on the Gold Initiative for Chronic Obstructive Lung Disease (GOLD) executive summary statement, as follows: 1. post-bronchodilator FEV1 < 30 % predicted or FEV1 < 50 % predicted + chronic respiratory failure, (chronic respiratory failure is defined as $PaO_2 < 60$ mm Hg with or without $PaCO_2 > 50$mm Hg while breathing air at sea level), 2. post-bronchodilator FEV1/FVC < 0.70, (k) patient has severe congestive heart failure (CHF) defined as New York Heart Association Functional Classification, Level IV.

Cognitive Assessments

Patients were evaluated for preoperative cognitive function by Mini Mental State Examination (MMSE) (43), Clinical Dementia Rating (CDR) (73), and history of dementia on the Charlson Comorbidity Index questionnaire (74). Consensus Diagnostic Committee (CDC) consisting of two psychiatrists and one geriatrician arrived at a consensus CDR score based on the information gathered from the informant.

Delirium Assessments

Delirium assessments were completed by trained research assistants who administered MMSE, Confusion Assessment Method (CAM) (58), Digit Span, and Delirium Rating Scale-Revised-98 (DRS-R-98) (41) preoperatively, and then daily from postoperative day (POD) 1 to POD 5 or up to the time of hospital discharge. They also interviewed the patient, family, nurse and reviewed medical records including physician notes.

Delirium Diagnosis

Consensus Diagnostic Committee (CDC) arrived at a consensus diagnosis of delirium based on the data collected by the research assistants. For this study, a patient was classified to have postoperative delirium if he or she had CDC adjudicated delirium diagnosis at any time during the postoperative period (Table IV.1). The diagnosis of subsyndromal delirium was given if the clinical scenario did not meet all three criteria for delirium, but one or two of the criteria were met.

Analyses

Laboratory Analyses

CSF samples were collected during routine spinal anesthesia, aliquoted and stored at – 80 F. Previously unthawed CSF samples were analyzed for full-length amyloid-beta 42 ($A\beta_{42}$), total tau and tau phosphorylated on threonine 181 (p-tau181) using the XMAP based Innogenetics AlzBio3 kit run on the Bio-plex 200 (Luminex) system (75). Each sample was run in triplicate, and analyzed on the same plate. Based on previous experiments, intra-assay coefficients of variation for the plates used in this study are 3.4 % $A\beta_{42}$, 5.8 % total tau (t-tau), and 6.8 % phosphorylated tau 181 (p-tau181_{181}). Inter-assay (plate to plate) coefficients of variation for a single CSF standard study are 8.3 % $A\beta_{42}$, 6.9 % t-tau, 9.3 % p-tau181_{181}.

Statistical Analyses

We conducted a series of risk factor comparisons of selected preoperative variables between those without delirium (no delirium group) and those with delirium (delirium group). Student's t-test was used for continuous variables and Fisher's exact test was used for categorical or binary variables. Age variable was examined both as a continuous variable and as a categorical variable (age categories: 7th decade ≥ 70 and < 80; 8th decade ≥ 80 and < 90; 9th decade ≥ 90). MMSE was examined as a continuous variable and as a dichotomous variable (<24, ≥ 24), with ≥ 24 being considered as being in the normal range (43). Variables that were identified as independent risk factors (p ≤

0.10) of postoperative delirium in the bivariate analysis and other variables from the literature were chosen for multivariable logistic regression. All analyses were conducted using STATA (StataCorp LP, College Station, TX).

RESULTS:

Baseline characteristics by postoperative delirium status

The overall incidence of delirium was 41 %. The mean age was 85 years, and approximately 1/3 were men. Most of the subjects were relatively healthy cognitively with greater than 2/3 of the cohort with MMSE $\geq$ 24 and very few with global Clinical Dementia Rating (CDR) score of $\geq$ 1. However, those in the delirium group had significantly lower preoperative MMSE and higher CDR Sum of Boxes (CDR-SB). There were no differences in the mean CSF biomarker levels of $A\beta_{42}$, t-tau, p-tau_{181} as well as $A\beta_{42}$/t-tau or $A\beta_{42}$/p-tau_{181} ratios between the two groups (Table IV.2).

Baseline characteristics by postoperative delirium status including subsyndromal delirium

When subsyndromal delirium cases were added to the delirium cases, the incidence of delirium increased to 58 %. The preoperative characteristics between the delirium and no delirium groups remained similar except for those with delirium had significantly higher proportions of individuals with higher global CDR scores as well as significantly higher proportion of individuals with MMSE $\leq$ 24. There were no differences in the mean CSF biomarker levels of $A\beta_{42}$, t-tau, p-tau181 as well as $A\beta_{42}$/t-tau or $A\beta_{42}$/p-tau181 ratios (Table IV.3).

Association of preoperative risk factors with postoperative delirium

In the bivariate analysis, preoperative MMSE and global CDR, CDR-SB were the only significant risk factors (Table IV.4). In the multivariable analysis, none of the variables remained significant (Table IV.5).

Association of CSF biomarkers with postoperative delirium by age categories

As the overall levels of CSF biomarkers were not significantly different between the delirium and no delirium groups, the data were stratified by age (decades). Although most subgroups did not show differences in the biomarker levels by delirium status, those in the 7th decade had lower preoperative levels of CSF Aβ_{42} in the delirium group compared to the no delirium group, albeit statistically not significant (Figure IV.1 and Table IV.6). Similar analysis was performed with CSF levels of t-tau and p-tau$_{181}$, but there were no differences between the two groups in any age subgroup (data not shown).

Association of CSF biomarkers with preoperative MMSE by age categories

Due to the fact that CSF biomarkers may be a better correlate of underlying cognitive function in younger (7th decade) patients, we performed an age stratified analysis examining the association between the preoperative levels of CSF biomarkers with preoperative cognitive MMSE scores. The CSF Aβ_{42} levels were significantly lower in those with lower (<24) MMSE group among the overall group and the 7th decade subgroup, but not in the 8th or in the 9th decade (Figure IV.2 and Table IV.7).

DISCUSSION:

In this study, we found that preoperative CSF levels of $A\beta_{42}$, t-tau, p-tau$_{181}$, $A\beta_{42}$/t-tau and $A\beta_{42}$/p-tau$_{181}$ ratios are not associated with postoperative delirium after hip repair surgery in a subsample of our study population. Our results show that there are no statistically significant differences in the preoperative CSF levels of the aforementioned biomarkers between the delirium group and no delirium group. However, we found that the CSF levels of $A\beta_{42}$ in the delirium group was lower compared to the no delirium group in a younger subgroup of patients (7th decade). In addition, the association of CSF levels of $A\beta_{42}$ with baseline cognitive measure with MMSE was strongest in the same age group.

Cognitive impairment is a well-known risk factor of postoperative delirium (60, 76). In our study, there was a trend towards lower preoperative MMSE score being associated with postoperative delirium, but not CSF biomarkers of AD. Our finding is similar to findings from a previous study of CSF AD biomarkers for predicting postoperative delirium in hip fracture population (77). However, these findings remain surprising as AD is thought to be highly prevalent in older adults, up to about a third among adults 85 and older (78, 79). CSF biomarkers such as lower levels of $A\beta_{42}$, higher levels of tau as well as their ratios have been shown to be well correlated with AD (31, 32) and are now part of recommended diagnostic work up in different stages of AD including preclinical and mild cognitive impairment (MCI) stages (28-30).

One of the reasons for the poor correlation of CSF biomarkers of AD and postoperative delirium may be that the association of these biomarkers with cognitive function may become attenuated with advancing age. One study showed that the association between AD pathology and dementia was strong at the age of 75, but was attenuated by age 95 (80). Another study of AD pathology by PET amyloid showed that amyloid (Aβ) positivity decreased with aging, especially in non-APOE4 carriers, suggesting that it was more helpful for AD diagnosis in earlier age (81).

In fact, our findings in a small subgroup of hip fracture patients demonstrate that there may be an age effect of CSF biomarkers in predicting postoperative delirium. CSF $A\beta_{42}$ levels are lower in the delirium group compared to the no delirium group among 70 year olds. In addition, there is a significant correlation between the clinical measure of cognitive function (MMSE) and CSF $A\beta_{42}$ among the same group, but not in the older age groups.

There are several limitation to this study. As this is an on-going randomized clinical trial, the intervention (light vs. heavy sedation) has not been unblinded, and therefore further analysis will need to be done once the treatment groups become known. The sample size is small as the CSF analysis was done on a subset of the cohort. Only limited clinical risk factors were examined due to the nature of the clinical trial.

The strengths of the study include the ability to examine the association between CSF biomarkers of AD and delirium in older adults including those in the 90's, which may allow further exploration of age effect on different CSF biomarkers. The outcome ascertainment of delirium is also a strength as it is very comprehensive in assessment and duration, and therefore is less likely to have missed an incident delirium.

Future studies will include association of CSF biomarkers with delirium severity as well as duration. In addition, plasma samples that were collected at the same time as CSF will be invaluable in allowing examination of peripheral vs. central biomarkers in delirium research. Current findings will also lead to future research into other non-AD biomarkers and risk factors including vascular risk factors.

Table IV.1. Delirium diagnostic criteria

Criterion	Description of each criterion
Criterion 1	Disturbance in Consciousness: (reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
Criterion 2	Change in Cognition: (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting dementia.
Criterion 3	Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

Delirium diagnosis was given by the Consensus Diagnostic Committee (CDC) if all three criteria are met. Subsyndromal delirium diagnosis was given if there is no delirium, but if one or two of the criteria are met.

Table IV.2. Baseline characteristics by postoperative delirium status

	Total (N=83)		No Delirium (N=48) 58%		Delirium (N=35) 41%		P-value
Demographics							
Age-years, mean (SD)	85	(7.3)	84	(7.3)	86	(7.4)	0.34
Male, n (%)	24	(28.9)	14	(29.2)	10	(28.6)	0.95
Race, n (%)	3	(3.6)	2	(4.2)	1	(2.9)	0.68
Education							0.14
Elementary	20	(24.1)	9	(18.8)	11	(31.4)	
High School	46	(55.4)	31	(64.6)	15	(42.9)	
College	17	(20.5)	8	(16.7)	9	(25.7)	
Cognitive Measures							
MMSE*, mean (SD)	24.7	(3.7)	25.5	(3.6)	23.6	(3.53)	**0.02**
MMSE < 24, n (%)	27	(32.5)	13	(27.1)	14	(40.0)	0.22
MMSE ≥ 24, n (%)	56	(67.5)	35	(72.9)	21	(60.0)	
CDR Global, N, (%)							
0	44	(53)	30	(62.5)	14	(40.0)	0.17
0.5	34	(41)	16	(33.3)	18	(51.4)	
1	4	(5)	2	(4.2)	2	(5.7)	
2	1	(1)	0	(0)	1	(2.9)	
CDR Sum of Boxes mean (SD)	0.98	(1.76)	0.58	(1.08)	1.54	(2.33)	**0.04**
CSF Laboratory Measures [b]							
Amyloid-beta 42 ($A\beta_{42}$) mean (SD)	355.15	(137.79)	346.74	(140.67)	367.28	(134.68)	0.50
total tau, mean (SD) [c]	85.39	(42.56)	84.55	(42.07)	86.51	(43.79)	0.84
p-tau181, mean (SD) [d]	23.97	(11.85)	23.48	(10.15)	24.31	(14.00)	0.76
$A\beta_{42}$/t-tau (SD)	5.25	(3.07)	5.15	(2.96)	5.38	(3.24)	0.74
$A\beta_{42}$/p-tau181 (SD)	20.01	(12.47)	19.16	(11.68)	21.15	(13.57)	0.49

[a] MMSE <15 excluded from the study; [b] CSF measures of amyloid-beta 42 (Aβ42), total tau (t-tau) and phosphorylated tau (p-tau181) are in the units of pg/ml. [c] 1 missing value of CSF t-tau from the “No Delirium” group; [d] 4 missing values of CSF p-tau181 from the “No Delirium” group and 2 from “Delirium” group (missingness of both t-tau and p-tau181 are due to the biomarker values being out of the range of detection limit).

Table IV.3. Baseline characteristics by postoperative delirium status including subsyndromal delirium

	Total (N=83)		No Delirium (N=34) 41%		Delirium [a] (N=49) 58%		P-value
Demographics							
Age-years, mean (SD)	85	(7.3)	84	(7.23)	86	(7.4)	0.23
Male, n (%)	24	(28.9)	9	(26.5)	15	(30.6)	0.68
Race, n (%)	3	(3.6)	2	(5.9)	1	(2.0)	0.46
Education							
Elementary	20	(24.1)	6	(17.6)	14	(28.6)	0.49
High School	46	(55.4)	21	(61.8)	25	(51.0)	
College	17	(20.5)	7	(20.6)	10	(20.4)	
Cognitive Measures							
MMSE, mean (SD)	24.7	(3.7)	26.4	(3.4)	23.4	(3.4)	**<0.001**
MMSE < 24, n (%)	27	(32.5)	6	(17.6)	21	(42.9)	**0.02**
MMSE ≥ 24, n (%)	56	(67.5)	28	(82.4)	28	(57.1)	
CDR Global, N, (%)							
0	44	(53)	25	(73.5)	19	(38.8)	**0.01**
0.5	34	(41)	7	(20.6)	27	(55.1)	
1	4	(5)	2	(5.9)	2	(4.1)	
2	1	(1)	0	(0)	1	(2)	
CDR Sum of Boxes mean (SD)	0.98	(1.76)	0.51	(1.18)	1.30	(2.02)	**0.03**
CSF Laboratory Measures							
Amyloid-beta 42 ($A\beta_{42}$) mean (SD)	355.15	(137.79)	362.96	(130.48)	349.74	(143.73)	0.67
total tau, mean (SD)	85.39	(42.56)	83.94	(37.60)	86.40	(46.11)	0.80
p-tau181, mean (SD)	23.97	(11.85)	23.71	(10.22)	23.92	(12.97)	0.94
$A\beta_{42}$/t-tau (SD)	5.25	(3.07)	5.22	(2.92)	5.26	(3.19)	0.94
$A\beta_{42}$/p-tau181 (SD)	20.01	(12.47)	1.98	(11.04)	1.98	(13.47)	0.86

[a] Delirium includes subsyndromal cases;

Table IV.4. Bivariate analysis of preoperative risk factors for postoperative delirium

	Total (N=83)	
Risk Factors	**Odds Ratio** (95% CI)	**P-value**
Demographics & BMI		
Age-years [a]	1.03 (0.97, 1.09)	0.34
Gender	1.03 (0.39, 2.69)	0.95
Race	0.58 (0.08, 3.97)	0.58
Education	0.90 (0.62, 1.29)	0.56
Cognitive Measures		
MMSE	0.86 (0.76, 0.98)	**0.02**
MMSE (<24, ≥ 24)	1.79 (0.71, 4.54)	0.22
CDR Global	4.25 (1.02, 17.64)	**0.05**
CDR Sum of Boxes	1.42 (1.02, 1.97)	**0.04**
CSF Laboratory Measures		
Amyloid-beta 42 ($A\beta_{42}$)	1.00 (0.99, 1.00)	0.50
total tau	1.00 (0.99, 1.01)	0.84
p-tau181	1.01 (0.97, 1.05)	0.76
$A\beta_{42}$/t-tau	1.02 (0.89, 1.18)	0.74
$A\beta_{42}$/p-tau181	1.01 (0.98, 1.05)	0.49

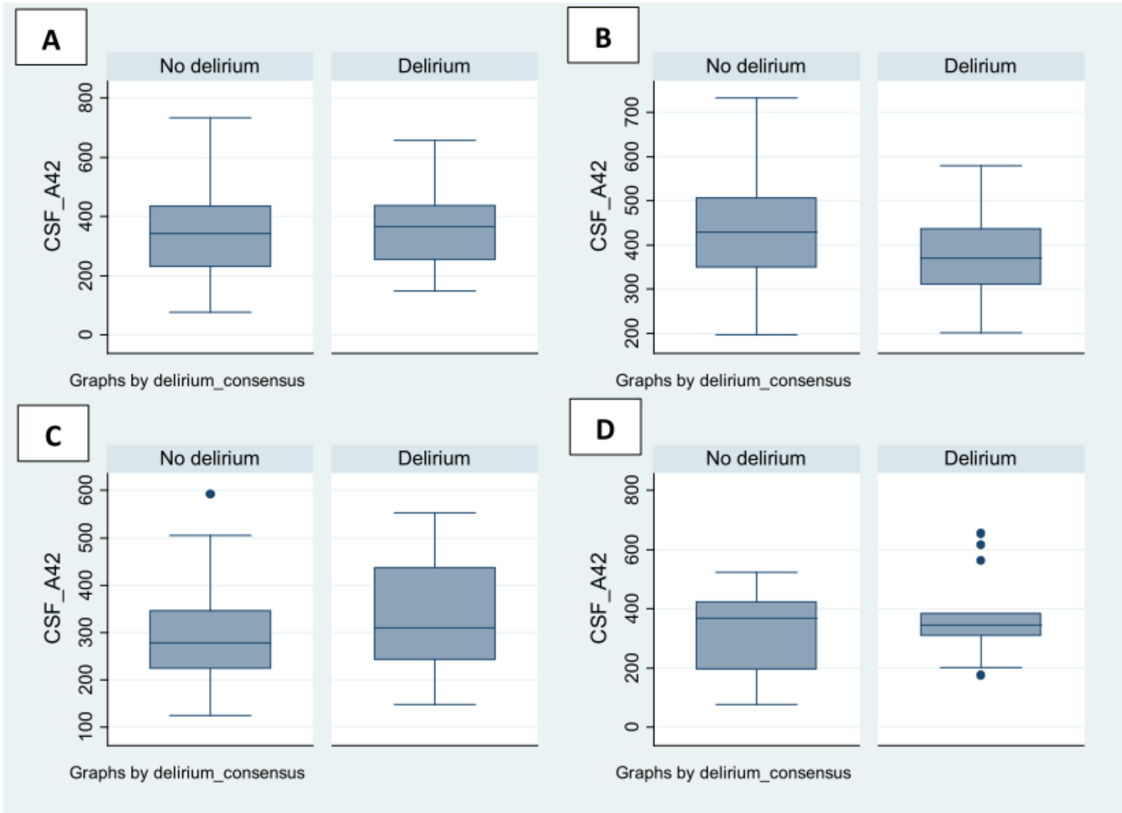
[a]Age as a categorical variable (decades) OR 1.04 (95% CI 0.62, 1.76) p-value=0.88

Table IV.5 Multivariable analysis of preoperative risk factors for postoperative delirium

	Total (N = 83)	
Risk Factors	**Odds Ratio** (95% CI)	**P-value**
Age	1.03 (0.94, 1.08)	0.83
Gender	1.32 (0.46, 3.76)	0.61
Race	0.42 (0.05, 3.64)	0.43
Education	1.29 (0.80, 2.10)	0.30
MMSE	0.84 (0.71, 1.01)	0.06 [a]
CDR-Global	2.26 (0.44, 11.69)	0.33

[a]P-value = 0.057

Figure IV.1. Age stratified comparison of CSF amyloid-beta 42 (Aβ42) levels by delirium status



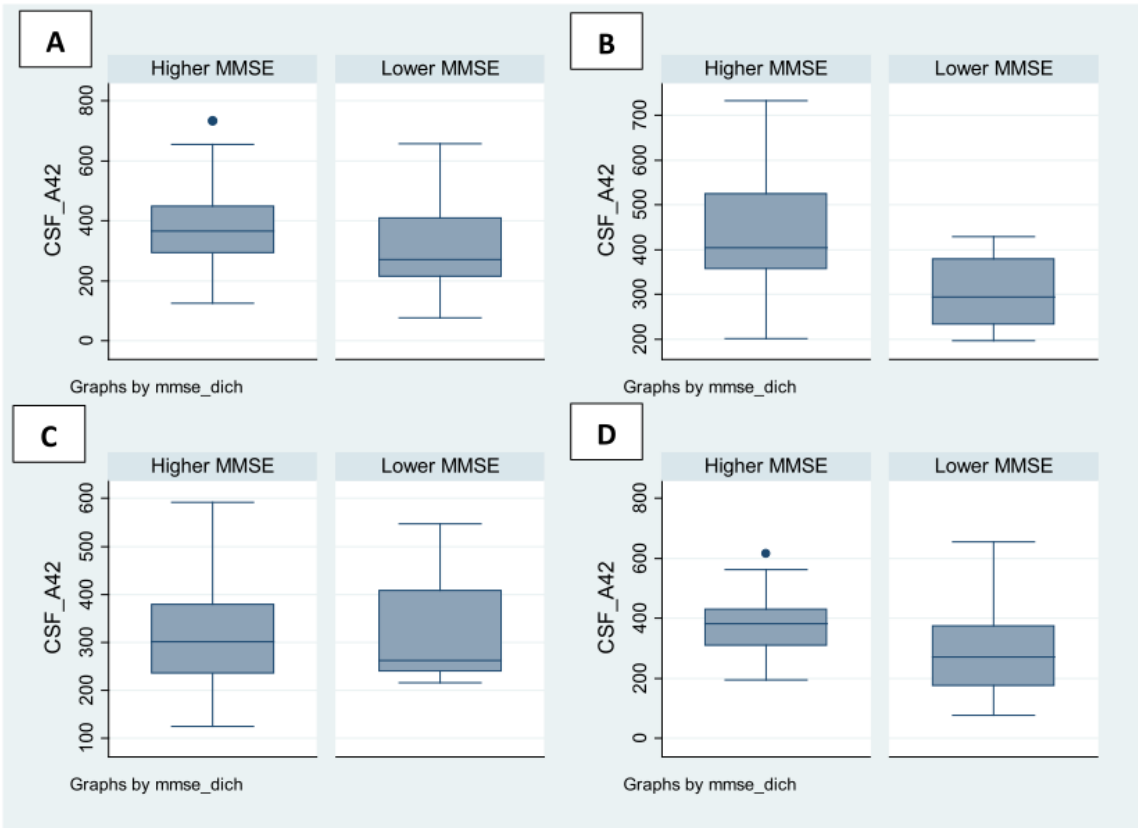
Comparison of CSF $A\beta_{42}$ levels between the groups that did not experience postoperative delirium "No delirium" and those that did "Delirium." (A) Overall group; (B) 7th decade; (C) 8th decade; (D) 9th decade.

Table IV.6. Age stratified comparison of CSF amyloid-beta 42 ($A\beta_{42}$) levels by delirium status

	CSF $A\beta_{42}$ Levels (pg/ml) (SD)			P-value
Age groups (decades)	**Total**	**No Delirium**	**Delirium**	
Overall No delirium N = 48[a] Delirium N = 35	355.15(137.79)	346.74(140.67)	367.28(134.68)	0.50
7th No delirium N = 13 Delirium N = 12	411.19(136.34)	441.50(151.67)	378.36(114.88)	0.26
8th No delirium N = 19 Delirium N = 10	319.10(124.13)	305.42(118.41)	345.10(136.91)	0.42
9th No delirium N = 15 Delirium N = 13	342.78(143.86)	315.78(135.62)	373.94(152.13)	0.29

[a.] One subject was in the 6th decade. Stratification of age by decades demonstrated that mean CSF $A\beta_{42}$ in those with postoperative delirium was lower compared to those without only among those in the 7th decade, although it did not reach a statistical significance. Lower CSF $A\beta_{42}$ is thought to be associated with Alzheimer's disease pathology.

Figure IV.2. Age stratified comparison of CSF amyloid-beta 42 (Aβ42) levels by MMSE status



Comparison of CSF $A\beta_{42}$ levels between the “Higher MMSE” (MMSE $\geq$ 24) and “lower MMSE” (MMSE < 24) (A) Overall group; (B) 7th decade; (C) 8th decade; (D) 9th decade. There were no significant differences in the CSF $A\beta_{42}$ levels between the Higher MMSE and Lower MMSE groups.

Table IV.7. Age stratified comparison of CSF amyloid-beta 42 ($A\beta_{42}$) levels by MMSE status

		CSF $A\beta_{42}$ Levels (pg/ml) (SD)		P-value
Age groups (decades)	**Total**	**Higher MMSE (MMSE ≥24)**	**Lower MMSE (MMSE<24)**	
Overall Higher MMSE N=57[a] Lower MMSE N=27	355.15(137.79)	377.13(133.81)	309.09(134.38)	**0.03**
7th Higher MMSE N=20 Lower MMSE N=5	411.19(136.34)	437.39(133.62)	306.38(97.73)	**0.05**
8th Higher MMSE N=20 Lower MMSE N=9	319.10(124.13)	317.95(130.42)	321.66(116.28)	0.94
9th Higher MMSE N=16 Lower MMSE N=13	342.78(143.86)	377.72(114.48)	301.43(163.53)	0.15

[a.] One subject was in the 6th decade. Lower CSF $A\beta_{42}$ is thought to be associated with Alzheimer's disease pathology.

APPENDIX

Appendix 1. Search terms for Chapter II

Hand-searched journals

Acta Anaesthesiologica Scandinavica, Age and Ageing, Anaesthesia Anesthesia and Analgesia, Anesthesiology, Canadian Journal of Anaesthesia, Clinical Orthopaedics and Related Research, Dementia and Geriatric Cognitive Disorders, Gerontology, International Journal of Geriatric Psychiatry, International Psychogeriatrics, Journal of Bone and Joint Surgery, Journal of the American Geriatrics Society (JAGS), Journals of Gerontology, New England Journal of Medicine, and the Journal of the American Medical Association

Hand-searched journal supplements

Anesthesiology, Acta Anaesthesiologica Scandinavica, Canadian Journal of Anaesthesia, JAGS, and Psychogeriatrics

PubMed Search Strategy

#1 “hip fractures” [mh] OR hip fracture* [All Fields] OR "hip" [mh] OR "hip" [All Fields] OR Subtrochanteric Fracture* [All Fields] OR Trochanteric Fracture* [All Fields] OR Intertrochanteric Fracture* [All Fields] OR “Femoral Neck Fractures” [mh] OR femoral neck fracture* [All Fields] OR Femur Neck Fracture* [All Fields]

#2 “delirium” [mh] OR “delirium” [All Fields] OR “delirium, dementia, amnestic, cognitive disorders” [mh] OR organic mental disorder* [All Fields] OR “traumatic psychosis” [All Fields] OR “nonpsychotic organic brain syndrome”

[All Fields] OR ("mental disorders"[mh] AND ("1969/01/01"[PDAT] : "1974/12/31"[PDAT])) OR “Confusion” [mh] OR cognitive defect* OR cognitive disorder* OR cognitive deficit* OR “cognitive dysfunction” OR cognitive impairment* OR organic brain syndrome* OR organic brain disease* OR “disorientation” [All Fields] OR organic brain disorder* [All Fields] OR confus* [All Fields] OR delir* OR “psychosis” [All Fields] OR “Intraoperative complications” [mh] OR Intraoperative complication* [All Fields] OR intra-operative complication* [All Fields] OR perioperative complication* [All Fields] OR peri-operative complication* [All Fields]

#3 “Orthopedics” [mh] OR orthopedic* [All Fields] OR orthopaedic* [All Fields] OR “Surgical Procedures, Operative” [mh] OR operative procedure* [All Fields] OR “surgery” [All Fields] OR “surgery” [subheading] OR “surgeries” [All Fields] OR “surgical” [All Fields] OR surgi* [All Fields] OR “monitoring, intraoperative” [mh] OR “intraoperative monitoring” [All Fields] OR “intra-operative monitoring” [All Fields] OR “intraoperative period” [mh] OR intraoperative period* [All Fields] OR intra-operative period* [All Fields] OR “intraoperative care” [mh] OR “intraoperative care” [All Fields] OR “intra-operative care” [All Fields] OR “perioperative care” [All Fields] OR “peri-operative care” [All Fields]

#4 #1 AND #2 AND #3

Embase Search Strategy

#1 'hip fracture'/exp OR 'hip fracture' OR 'hip fractures' OR 'femur subtrochanteric fracture'/exp OR subtrochanteric NEAR/2 fracture* OR 'femur intertrochanteric fracture'/exp OR intertrochanteric NEAR/2 fracture* OR 'femur fracture'/exp OR femoral NEAR/2 fracture* OR 'trochanteric fracture' OR 'trochanteric fractures' OR 'hip'/exp OR 'hip': ab, ti

#2 'delirium'/exp OR delirium OR 'cognitive defect'/exp OR 'cognitive defect' OR 'cognitive defects' OR 'cognitive disorder' OR 'cognitive disorders' OR 'cognitive deficit' OR 'cognitive deficits' OR 'cognitive dysfunction' OR 'cognitive impairment' OR 'cognitive impairments' OR 'organic mental disorder' OR 'organic mental disorders' OR 'traumatic psychosis' OR 'nonpsychotic organic brain syndrome' OR 'organic brain syndrome'/exp OR 'organic brain syndrome' OR 'organic brain disease' OR 'confusion'/exp OR confusion OR 'disorientation' OR 'organic brain disorder' OR 'organic brain disorders' OR confus* OR delir* OR 'psychosis'/exp OR 'psychosis' OR intraoperative AND ('complication'/exp OR complication) OR 'intraoperative complication' OR 'intraoperative complications' OR 'intra-operative complication' OR 'intra-operative complications' OR 'perioperative complication' OR 'perioperative complications' OR 'peri-operative complication' OR 'peri-operative complications'

#3 'orthopedics'/exp OR 'orthopedic' OR 'orthopedics' OR 'orthopaedic' OR 'orthopaedics' OR 'orthopedic surgery'/exp OR 'surgery'/exp OR 'surgery' OR surgi* OR 'operative procedure' OR 'operative procedures' OR 'intraoperative period'/exp OR 'intraoperative period' OR 'intraoperative periods' OR 'intra-operative complication' OR 'intra-operative complications' OR 'perioperative period'/exp OR 'perioperative period' OR 'perioperative periods' OR 'perioperative complication'/exp OR 'perioperative complication' OR 'perioperative complications' OR 'peri-operative complication' OR 'peri-operative complications'

#4 #1 AND #2 AND #3

PsycINFO Search Strategy

S1 DE "Hips" OR hip fracture* OR femoral neck fracture* OR hip OR hips

S2 DE "Delirium" OR DE "Organic Brain Syndromes" OR organic brain syndrome* OR organic mental disorder* OR DE "mental confusion" OR DE "cognitive impairment" OR cognitive impairment* OR cognitive defect* OR cognitive disorder* OR cognitive deficit* OR "cognitive dysfunction" OR organic brain disease* OR disorientation OR organic brain disorder* OR confus* OR delir* OR DE "psychosis" OR psychosis

S3 Orthopedics OR orthopedic OR operative procedure* OR DE "surgery" OR surgery OR surgeries OR surgi*

S4 S1 AND S2 AND S3

CINAHL Search Strategy

S1 (MM "Hip") OR hip* OR (MM "Hip Fractures, Stress") OR (MM "Hip Fractures")
OR (MM "Hip Surgery") OR subtrochanteric fracture* OR trochanteric fracture* OR femoral neck fracture* OR (MM "femur neck") OR femur neck fracture*

S2 (MM "Delirium") OR (MM "Delirium, Dementia, Amnestic, Cognitive Disorders") OR (MM "Organic Mental Disorders") OR (MM "Confusion") OR (MM "Acute Confusion (NANDA)") OR (MM "Cognition Disorders") OR (MM "Intraoperative Complications") OR (MM "Intraoperative Care") OR confus* OR delir* OR organic mental disorder* OR cognitive defect* OR cognitive disorder* OR cognitive deficit* OR "cognitive dysfunction" OR cognitive impairment* OR organic brain syndrome* OR organic brain disease* OR disorientation OR organic brain disorder* OR intraoperative complication* OR intraoperative care OR intra-operative complication* OR intra-operative care OR perioperative complication* OR peri-operative complication*

S3 (MM "Orthopedics") OR orthopedic* OR orthopaedic* OR (MM "Orthopedic Surgery") OR (MM "Hip Surgery") OR (MM "Surgery, Operative") OR surgi* OR operative procedure* OR “surgery” OR "surgeries" OR “intraoperative monitoring” OR “intraoperative period” OR “intraoperative care”

S4 S1 AND S2 AND S3

Cochrane Library Search Strategy

#1 MeSH descriptor: [Hip Fractures] explode all trees

#2 MeSH descriptor: [Arthroplasty, Replacement, Hip] explode all trees

#3 intra-articular fracture* or periprosthtic fracture* or hip* or femoral neck fractures or subtrochanteric fracture* or trochanteric fracture* or intertrochanteric fracture* or femur neck fracture*:ti,ab,kw

#4 #1 or #2 or #3

#5 MeSH descriptor: [Delirium] explode all trees

#6 MeSH descriptor: [Delirium, Dementia, Amnestic, Cognitive Disorders] explode all trees

#7 MeSH descriptor: [Confusion] explode all trees

#8 organic mental disorder* or confus* or disorientation or "organic brain disorder" or "organic brain disorders" or delir* or "psychosis" or "intraoperative complications" or "intraoperative complication" or "intra-operative complication" or "intra-operative complications" or "perioperative complication" or "perioperative complication" or "peri-operative complications" or "peri-operative complications":ti,ab,kw

#9 MeSH descriptor: [Intraoperative Complications] explode all trees

#10 #5 or #6 or #7 or #8 or #9

#11 MeSH descriptor: [Orthopedics] explode all trees

#12 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#13 MeSH descriptor: [Intraoperative Period] explode all trees

#14 MeSH descriptor: [Intraoperative Care] explode all trees

#15 MeSH descriptor: [Perioperative Period] explode all trees

#16 MeSH descriptor: [Perioperative Care] explode all trees

#17 MeSH descriptor: [Monitoring, Intraoperative] explode all trees

#18 Orthopedic* or orthopaedic* or "operative procedure" or "operative procedures" or surgery or surgeries or surgi* or "intraoperative monitoring" or "intra-operative monitoring" or "intraoperative period" or "intra-operative period" or "intraoperative care" or "intra-operative care" or "intraoperative period" or "intraoperative period" or "perioperative period" or "peri-operative period" or "perioperative care" or "peri-operative care":ti,ab,kw

#19 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18

#20 #4 and #10 and #19

<u>Hand Search Strategy</u>

“Subtrochanteric Fracture,” “Trochanteric Fracture,” “Intertrochanteric Fracture,” “Femoral Neck fracture”

“confusion,” “disorientation”

“surgery,” “operation,” “intraoperative,” “perioperative,” “preoperative”

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77. Witlox J, Kalisvaart KJ, de Jonghe JF et al. Cerebrospinal fluid beta-amyloid and tau are not associated with risk of delirium: a prospective cohort study in older adults with hip fracture. J Am Geriatr Soc 2011; 59:1260-1267.

78. Hebert LE, Weuve J, Scherr PA et al. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 2013; 80:1778-1783.

79. Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Alzheimers Dement 2015; 11:332-384.

80. Savva GM, Wharton SB, Ince PG et al. Age, neuropathology, and dementia. N Engl J Med 2009; 360:2302-2309.

81. Ossenkoppele R, Jansen WJ, Rabinovici GD et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. Jama 2015; 313:1939-1949.

CURRICULUM VITAE FOR ACADEMIC PROMOTION

The Johns Hopkins University School of Medicine

Esther S. Oh, MD April 4, 2016

DEMOGRAPHIC INFORMATION

Current Appointments

2008 – present	Assistant Professor, Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine
2008 – present	Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine (Joint Appointment)
2014 – present	Division of Neuropathology, Department of Pathology, Johns Hopkins School of Medicine (Secondary Appointment)

Personal Data

Division of Geriatric Medicine and Gerontology

Department of Medicine

Mason F. Lord Center Tower

5200 Eastern Avenue, 7th Floor

Baltimore, MD 21224

(410) 550-1318 (office telephone)

(410) 550-8701 (office fax)

e-mail: eoh9@jhmi.edu

Pager (410) 283-8578

Fluent English, Korean, conversational Japanese

Education and Training

Undergraduate

1991	B.S., Biochemistry, University of Rochester, Rochester, NY

Doctoral/graduate

1998	M.D., Finch University of Health Sciences, the Chicago Medical School, Chicago, IL
2010	Ph.D. candidate, Graduate Training Program in Clinical Investigation (GTPCI), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Postdoctoral

1998 – 2001	Resident, Internal Medicine, University of Illinois at Chicago, Chicago, IL
2001 – 2002	Chief Resident, Internal Medicine, University of Illinois at Chicago, Chicago, IL
2002 – 2005	Clinical and Research Fellowship, Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, Baltimore, MD

Professional Experience

1990 – 1990	Student Researcher, Department of Neurobiology and Anatomy, University of Rochester, Rochester, NY
1990 – 1991	John A. Hartford Foundation Student Researcher, Molecular Neurobiology Section, National Institute on Aging (NIA)/National Institutes of Health (NIH), Baltimore, MD
1991 – 1992	Student Researcher, Department of Molecular Microbiology, Okayama University, Okayama, Japan

1993 – 1994	Biologist, Department of Molecular Cell Biology, American Type Culture Collection (ATCC), Rockville, MD
1995 – 1995	Student Researcher, National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH), Bethesda, MD
2002 – 2005	Postdoctoral Fellow, Division of Geriatric Medicine and Gerontology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
2005 – 2008	Instructor, Division of Geriatric Medicine and Gerontology, Department of Medicine (primary appointment), Division of Neuropathology, Department of Pathology (secondary appointment), Johns Hopkins University School of Medicine, Baltimore, MD
2007 – present	Investigator, Clinical Core, Johns Hopkins Alzheimer's Disease Research Center
2008 – present	Assistant Professor, Division of Geriatric Medicine and Gerontology, Department of Medicine (primary appointment), Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD
2014 – present	Assistant Professor, Division of Neuropathology, Department of Pathology (secondary appointment), Johns Hopkins University School of Medicine, Baltimore, MD

PUBLICATIONS

Original Research

1. Tabuchi A, Sano K, **Oh E**, Tsuchiya T, Tsuda M. Modulation of AP-I activity by nitric oxide (NO) *in vitro*: NO-mediated modulation of AP-I. FEBS Letters, 1994; 351:123-127.
2. Ohtani K, Sakurai H, **Oh E**, Iwata E, Tsuchiya T, Tsuda M. Involvement of protein kinase C in calcium signaling pathway to activation of AP-I DNA-binding activity evoked via NMDA and voltage-gated calcium channels. Journal of Neurochemistry, 1995; 65(2):605-614.
3. Tabuchi A, **Oh E**, Taoka A, Sakurai H, Tsuchiya T, and Tsuda M. Rapid attenuation of AP-I transcriptional factors associated with nitric oxide (NO) – mediated neuronal cell death. The Journal of Biological Chemistry, 1996; 271: 31061-31067.
4. **Oh ES**, Savonenko AV, King JF, Fangmark Tucker SM, Rudow GL, Xu G, Borchelt DR, Troncoso JC, Amyloid precursor protein increases cortical neuron size in transgenic mice. Neurobiology of Aging, 2009; 30(8):1238-1244. PMID 18304698 PMCID 2796369.

5. **Oh ES***, Mielke MM, Rosenberg PB, Jain A, Fedarko NS, Lyketsos CG, Mehta PD. Comparison of conventional ELISA with electrochemiluminescence technology for detection of amyloid-beta (Aβ) in plasma. Journal of Alzheimer's Disease, 2010; 21(3):769-773. PMID 20634583 PMCID 255878. *corresponding author
6. Liu Y, Lee MK, James MM, Price DL, Borchelt DR, Troncoso JC, **Oh ES***. Passive amyloid-β immunotherapy attenuates monoaminergic axonal degeneration in APPswe/PS1dE9 mice. Journal of Alzheimer's Disease, 2010; 23(2):271-9. PMID 20966549 PMCID 3063938. *corresponding author
7. Rosenberg PB, Mielke MM, Appleby B, **Oh E**, Leoutsakous JM, Lyketsos CG. Neuropsychiatric symptoms in MCI subtypes: the importance of executive dysfunction. International Journal of Geriatric Psychiatry, 2011; 26(4):364-372. PMID 20845402 PMCID 3204866
8. Rosenberg PB, Mielke MM, Appleby B, **Oh E**, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incidence of dementia and Alzheimer's disease. The American Journal of Geriatric Psychiatry. 2013 Jul; 21(7):685-695. PMID 22546695 PMCID 3428504
9. Parker DC, Mielke MM, Yu Q, Rosenberg PB, Jain A, Lyketsos CG, Fedarko NS, **Oh ES***. Plasma neopterin level as a marker of peripheral cellular immune activation in amnestic mild cognitive impairment (aMCI) and Alzheimer's disease. International Journal of Geriatric Psychiatry, 2013; 28(2):149-154. PMID 22539447 PMCID3505262 *corresponding author
10. Yokoi Y, Misal M, **Oh E**, Bellantoni M, Rosenberg B. Benzodiazepine discontinuation and patient outcome in a chronic geriatric medical/psychiatric unit: A retrospective chart review. Geriatrics and Gerontology International, 2014 Apr; 14(2):388-394. PMID 24666628
11. **Oh ES***, Li M, Fafowora T, Inouye S, Chen C, Rosman L, Lyketsos C, Sieber F, Puhan M. Preoperative risk factors for postoperative delirium following hip fracture repair: A systematic review. International Journal of Geriatric Psychiatry, 2015; 30(9):900-910. PMID 25503071 PMCID 4465414 *corresponding author
12. Hshieh T, Yue J, **Oh E**, Puelle M, Dowell S, Travison T, Inouye S. Effectiveness of Multi-component non-pharmacologic delirium interventions: A systematic review and meta-analysis. JAMA Internal Medicine. 2015 Apr; 175(4):512-520. PMID 25643002 PMCID 4388802
13. Holroyd K, Fosdick L, Smith G, Leoutsakos J, Munro C, **Oh, ES**, Drake K, Rosenberg P, Anderson S, Salloway S, Burke A, Wolk D, Tang-Wai D, Ponce F, Assad W, Okun M, Baltuch G, Foote K, Targum S, Lozano A, Lyketsos C. Deep brain stimulation targeting the fornix for mild Alzheimer Dementia: design of the ADvance randomized controlled trial. Open Access Journal of Clinical Trials. 2015 July; 2015 (7):63-76 (Clinical Trial – role in manuscript writing)
14. Lee JL, **Oh ES**, Lee RW, Finucane TE. Serum albumin and prealbumin in calorically-restricted, non-diseased individuals: a systematic review. The American Journal of Medicine. 2015 Sept; 128(9):1023.e1-1023.e22 PMID25912205
15. **Oh ES***, Marano CM, Leoutsakos JM, Lee RW, Rissman RA, Smith GS, Craft S, Lyketsos CG, Oral glucose tolerance testing to modulate plasma amyloid levels: A novel biomarker. Alzheimer's and Dementia: Diagnosis, Assessment & Disease Monitoring, the journal of the Alzheimer's Association. 2015 Sep; 1(3):311-315. PMID 26413562 PMCID 4578701
16. Neufeld KJ, Leoutsakos JS, **Oh E**, Sieber FE, Chandra A, Ghosh A, Schretlen DJ, Needham, DM. Long-term outcomes of older adults with and without delirium

immediately following recovery from general anesthesia for surgery. The American Journal of Geriatric Psychiatry. 2015 Oct; 23(10):1067-1074. American Journal of Geriatric Psychiatry, PMID 25912784

17. Ponce FA, Asaad W, Foote KD, Anderson WS, Cosgrove GR, Baltuch GH, Beasley K, Fosdick L, **Oh ES**, Targum SD, Smith GS, Lyketsos CG, Lozano AM, Bilateral fornix deep brain stimulation for Alzheimer's disease: surgical safety in the ADvance Trial. Journal of Neurosurgery. 2015 Dec 18:1-10 (epub). PMID 26181976 (Clinical Trial – role in data analysis, manuscript writing)
18. Kavouspour C, Wang NY, Mears S, **Oh ES**, Sieber FE, Surgical procedure and postoperative delirium in geriatric hip fracture patients. European Journal of Anaesthesiology. 2016 Mar; 33(3):230-231. PMID 26203972
19. **Oh ES***, Sieber F, Leoutsakos JM, Inouye S, Lee HB, Sex differences in hip fracture surgery: preoperative risk factors of delirium and postoperative outcomes. The Journal of the American Geriatrics Society. (in press, 2016) *corresponding author
20. O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, Hall J, Zetterberg H, Lovestone S, Gupta V, Graff-Radford N, Martins R, Jeromin A, Waring S, **Oh E**, King M, Baker L & Hampel H for the ISTAART Blood Based Biomarker Professional Interest Area. Comparing biological markers of Alzheimer's disease across blood fraction and platforms: Comparing apples to oranges. Alzheimer's and Dementia: Diagnosis, Assessment & Disease Monitoring, the journal of the Alzheimer's Association. (in press, 2016)

Review Articles

1. **Oh ES***, Troncoso JC, Fangmark-Tucker SM. Maximizing the potential of plasma amyloid-beta as a diagnostic biomarker for Alzheimer's disease. Neuromolecular Medicine, 2008;10(3):195-207. PMID 18543125 PMCID 2558671. *corresponding author
2. <u>Mamo SK</u>, Reed NS, Nieman CL, **Oh ES**, Lin FR, Sound amplifiers for adults with hearing loss. The American Journal of Medicine. 2016 Mar;129(3):245-250 PMID 2649871 PMCID 4755807
3. Contrera K**,** Wallhagen M, <u>Mamo S</u>, **Oh ES**, Lin FR, Hearing Health Care of Older Adults 2015. the Journal of the American Board of Family Medicine (in press, 2016)

Book Chapters, Monographs

1. **Oh ES**, Lyketsos CG, Wong PC, Mouse models of Alzheimer's disease. *Principles and Practice of Geriatric Psychiatry, 3rd Ed.* Wiley-Blackwell, 2011
2. Heffernan S, **Oh E**, Lyketsos C, Neufeld K, Delirium. *Troublesome Disguises - Managing Challenging Disorders in Psychiatry, 2nd Ed.* Wiley-Blackwell, 2014

Other Publications

Guidelines/Protocols, Consensus Statement, Expert Opinion, Consortium Articles

1. AGS/NIA Delirium Conference Writing Group, Planning Committee and Faculty. The American Geriatrics Society/National Institute on Aging Bedside-to-Bench Conference: Research Agenda on Delirium in Older Adults. Journal of the American Geriatrics Society. 2015 May; 63:843-852. PMID 25834932

Editorials

1. Amjad H, **Oh E**. Invited commentary on Booker et al., Clarifying Dementia Risk Factors: Treading in Murky Waters. International Psychogeriatrics. (in press 2016).

Other Media – Electronic Print

1. **Oh E**, A Case of Depression in a Patient with Dementia [educational module for Johns Hopkins Geriatric Education Center] 2006 (http://www.hopkinsmedicine.org/gec/studies/depression_dementia.html)
2. **Oh E**, Detection of Cognitive Impairment in Primary Care Setting (educational module for Johns Hopkins Geriatric Education Center) 2013 http://webcast.jhu.edu/Mediasite/Play/a72bb63215dc4c94b075f0dc5d1ea6581d
3. Gabbard J, David S, McNabney, M, **Oh E**. Postoperative Delirium. The SCORE (Surgical Council on Resident Education) Portal 2015 http://www.surgicalcore.org

   * The educational module developed for the SCORE is part of a peer-reviewed national educational curriculum for residents in general surgery and related specialties. All but two surgical residencies in the U.S. use the SCORE as part of the core curriculum. The site averages 60,500 logins per month.

Other Media – Internet

1. **Oh, E**, Glucose tolerance and dementia, October 2nd, 2015, Johns Hopkins Medicine Podcasts http://podcasts.hopkinsmedicine.org/2015/09/25/october-2-2015-glucose-tolerance-and-dementia/#.VhhAaClsN-k.mailto
2. **Oh,** E, November 28th, 2012, Diabetes and Alzheimer's disease http://www.lifelivedforward.com/2012/11/28/diabetes-alzheimers-disease

FUNDING

Extramural Funding

Research Extramural Funding

Current:

08/21/2015-04/30/2016	Therapeutic Effect of Intranasal Insulin on Cognition, Function, and AD Biomarker RF1AG041845 NIA / NIH $154,335 Site PI: Oh Role: Site Principal Investigator (effort subsumed under K23)
9/30/2012-8/31/2017	CSF Predictors of Postoperative Delirium in Non-demented Hip Fracture Patients 1K23AG043504-01 NIA / NIH $818,775 PI: Oh Role: Principal Investigator, 75% effort
Pending:	A Pro-Inflammatory Endophenotype to Predict Treatment Response to NSAID Therapy in Alzheimer's disease R01 NIA / NIH PI: Sid O'Bryant Role: Co-investigator, 10% effort
	A Randomized Double Blind Placebo Controlled Trial of Ramelteon in the Prevention of Postoperative Delirium in Older Patients Undergoing General Anesthesia R21 NIA / NIH PI: Karin Neufeld Role: Co-investigator, 10% effort

Previous:

6/15/10-5/30/14	Oral Glucose Tolerance Test for Alzheimer's Disease Biomarker Development

R21AG033769
NIA / NIH
$368,232
PI: Oh, Co-PI: Craft

Role: Principal Investigator

07/01/12-6/30/2014	Geriatric Education Centers-Supplement HRSA 5 UB4HP19193-03 $ 2,177,718 PI: Burton Role: Co-investigator, 7.5% effort
7/01/09-6/30/12	Oral Glucose Tolerance Test for Alzheimer's Disease Biomarker Development The Rosalinde and Arthur Gilbert Foundation/AFAR New Investigator Award in Alzheimer's disease $75,000 PI: Oh Role: Principal Investigator, 25% effort (effort subsumed under KL2)
7/1/10-6/31/12	Institute for Clinical and Translational Research (KL2) 5KL2RR025006 National Center for Advancing Translational Sciences (NCATS)/NIH $3,293,594 PI: Ford Role: The Johns Hopkins Clinical Research Scholar, 80% effort
09/01/09-03/31/11	Alzheimer's Disease and Animal Models Project 2 (Troncoso, Project Leader)

	P50 AG05146 NIA /NIH $219,749 PI: Price Role: Faculty, 5% effort
07/07 – 06/08	Biomarker Development for Alzheimer's Disease 2007-0005 Hartford Center of Excellence Renewal $100,000 PI: Durso Role: Hartford Scholar, 21% effort
04/05 – 04/07	Research Supplement to Promote Diversity in Health-Related Research P50 AGO05146 NIA / NIH $189,790 PI: Price Role: Co-Investigator, 75% effort
07/05 – 06/07	Use of a Biotinylated Anti-Aβ Antibody to Diagnose Early States of Alzheimer's Disease Fidelity Foundation $73,318 PI: Oh Role: Principal Investigator, 5% effort

Intramural Funding

Research Intramural Funding:

09/01/2014-08/31/2015	Reducing the Symptom Burden of Cognitive Impairment through Affordable and Accessible Hearing Health Care The Johns Hopkins Alzheimer's Disease Research Center Pilot Grant $26,432 PI: Lin Role: Co-investigator (effort subsumed under K23)
04/30/2014-04/30/2015	Providing Hearing Health Care to Patients at the Johns Hopkins Memory Clinic Institute for Clinical and Translational Research Accelerated Translational Incubator Pilot (ATIP) Program $35,000 PI: Lin Role: Co-investigator (effort subsumed under K23)

CLINICAL ACTIVITIES

Clinical Focus

My main clinical focus at the Johns Hopkins Memory and Alzheimer's Treatment Center (JHMATC) is evaluation and treatment of cognitive impairment and associated disorders including, but not limited to the following disorders.

- Mild Cognitive Impairment (MCI), Alzheimer's dementia (AD), Dementia of Lewy Bodies (DLB), Frontotemporal dementia (FTD)
- Preoperative cognitive assessment
- Postoperative cognitive dysfunction (POCD)
- Behavioral and psychological symptoms of dementia (BPSD)
- Delirium
- Multi-morbidity and polypharmacy associated with cognitive disorders

My clinical role as a clinician in the Division of Geriatric Medicine and Gerontology also includes, but not limited to the following:

- Perioperative consultation
- Evaluation and treatment of patients in the Specialty Hospitals at the Johns Hopkins Bayview Medical Center (JHBMC)
- Evaluation and treatment of patients on the in-patient general internal medicine units at the Johns Hopkins Bayview Medical Center (JHBMC)

Medical, other state/government licensure

2003 – present Maryland # D60628

Boards, other specialty certification

2013 American Board of Internal Medicine Maintenance of Certification (MOC)

2014 American Board of Geriatric Medicine Maintenance of Certification (MOC)

Clinical Service Responsibilities

2005 – present Internal Medicine Service, Attending Physician, Johns Hopkins Bayview Medical Center (JHBMC), 4 weeks per year (2 week rotations)

Clinical Program Building/Leadership

2008 – present Associate Director, The Johns Hopkins Memory and Alzheimer's Treatment Center (JHMATC). In my capacity, I am responsible for overseeing the clinical operation at the JHMATC along with the Director and the Co-Directors.

01/08 – 06/10 Assistant Medical Director, Medical Behavior Unit (MBU), Johns Hopkins Bayview Medical Center Specialty Hospitals

EDUCATIONAL ACTIVITIES

Educational Focus

My main educational focus is on evaluation and treatment of cognitive impairment and associated disorders, encompassing learners from medical school, residency, postdoctoral fellowship, as well as physicians and caregivers. These educational activities vary from individual instructions in clinic settings to larger Continuing Medical Education (CME) settings.

Teaching

Classroom Instruction

2001 – 2002	Instructor, internal medicine residents, ambulatory curriculum, University of Illinois at Chicago (UIC), Chicago, IL.
2001 – 2002	Instructor, third year medical students, ambulatory curriculum, Jesse Brown VA Medical Center (formerly the West Side VA Medical Center) rotation, University of Illinois at Chicago (UIC), Chicago, IL.
2001 – 2002	Instructor, third year medical students, monthly lectures on “Asthma” and “Diabetes,” University of Illinois at Chicago (UIC), Chicago, IL.
2001 – 2002	Instructor, third year medical students, monthly lectures on “Dementia” and visit to the Alzheimer's Family Day Care Center, University of Illinois at Chicago (UIC), Chicago, IL.
2009	Instructor, physicians participating in the Johns Hopkins Division of Geriatric Medicine and Gerontology Mini-Fellowship, Baltimore, MD
2014 – present	Faculty discussant, postdoctoral fellows, Journal Club, Johns Hopkins Division of Geriatric Medicine and Gerontology, Baltimore, MD.

Clinical Instruction

2005 – present	Attending physician, internal medicine residents, Johns Hopkins Bayview Medical Center, Baltimore, MD.
2005 – 2008	Attending physician, medical students and residents, Geriatric Psychiatry Memory Clinic, Johns Hopkins Hospital, Baltimore, MD.
2005 – 2006	Attending physician, medical students, residents and postdoctoral fellows, Terrace Rehabilitation, Johns Hopkins Bayview Medical Center, Baltimore, MD.

2007	Attending physician, medical students, residents and postdoctoral fellows, Hip Fracture Consult Service, Johns Hopkins Bayview Medical Center, Baltimore, MD.
2007 – 2008	Attending physician, Chesapeake Chronic Medical Unit, medical students and postdoctoral fellows, Johns Hopkins Bayview Medical Center, Baltimore, MD.
2008 – 2010	Attending physician, Medical Behavior Unit (formerly - Medical Psychiatry Unit), medical students and postdoctoral fellows, Johns Hopkins Bayview Medical Center, Baltimore, MD.
2008 – present	Attending physician, medical students, residents and postdoctoral fellows, the Johns Hopkins Memory and Alzheimer's Treatment Center, Johns Hopkins Bayview Medical Center, Baltimore, MD.

CME Instruction

JHMI/Regional

04/12/08	Plenary Speaker, physicians and allied health care workers, "Diabetes, Insulin Resistance and Dementia: New Therapeutic Avenues?," 14th Annual Update on the Treatment of Alzheimer's and Related Disorders, Johns Hopkins University Department of Psychiatry and Behavioral Sciences CME, Baltimore, MD.
02/04/10	Instructor, physicians and allied health care workers, "Update on Dementia: What's on the Horizon," Edmund G. Beacham 37th Annual Current Topics in Geriatrics, Johns Hopkins University Division of Geriatric Medicine and Gerontology CME, Baltimore, MD.
04/10/10	Instructor, physicians and allied health care workers, "Medical Co-morbidity in Dementia Care," 16th Annual Update on The Treatment of Alzheimer's and Related Disorders, Johns Hopkins University Department of Psychiatry and Behavioral Sciences CME, Baltimore, MD.
04/02/11	Instructor, physicians and allied health care workers, "Using Cholinesterase Inhibitors and Memantine in Non-AD Dementia: Pros and Cons," 17th Annual Update on the Treatment of Alzheimer's and Related Disorders, Johns Hopkins University Department of Psychiatry and Behavioral Sciences CME, Baltimore, MD.
02/15/13	Instructor, physicians and allied health care workers, "Update on Dementia: What's on the Horizon," Edmund G. Beacham 40th Annual Current Topics in Geriatrics, Johns Hopkins University Division of Geriatric Medicine and Gerontology CME, Baltimore, MD.

04/13/13	Instructor, physicians and allied health care workers, “Handling After Hour Calls from Patients and Caregivers,” 19th Annual Update on the Treatment of Alzheimer’s and Related Disorders, Johns Hopkins University Department of Psychiatry and Behavioral Sciences CME, Baltimore, MD.
02/15/14	Instructor, physicians and allied health care workers, “Screening for Dementia in the Office,” Edmund G. Beacham 41th Annual Current Topics in Geriatrics, Johns Hopkins University Division of Geriatric Medicine and Gerontology CME, Baltimore, MD.
04/12/14	Instructor and Chair of the Plenary Panel on Agitation and Its Management, physicians and allied health care workers, “Helping the Patients with Dementia Decide When and How to Stop Driving,” 20th Annual Update on the Treatment of Alzheimer’s and Related Disorders, Johns Hopkins University Department of Psychiatry and Behavioral Sciences CME, Baltimore, MD..
02/26/15	Instructor, physicians and allied health care workers, “Is This Delirium?” Johns Edmund G. Beacham 42nd Annual Current Topics in Geriatrics, Johns Hopkins University Division of Geriatric Medicine and Gerontology CME, Baltimore, MD.
03/05/16	Instructor, physicians and allied health care workers, “Scan or not to Scan: Imaging Dementia-Evidence for Amyloid Scanning” Johns Edmund G. Beacham 43rd Annual Current Topics in Geriatrics, Johns Hopkins University Division of Geriatric Medicine and Gerontology CME, Baltimore, MD.

Workshops/Seminars

JHMI/Regional

11/01/08	Presenter, patients and caregivers, “Tips to Manage Alzheimer’s,” Journey to Hope Conference, Johns Hopkins University Bayview Medical Center, Baltimore, MD.
10/31/09	Presenter, patients and caregivers, “Sleeping, Eating and Bathroom Issues in Dementia,” Journey to Hope Conference, Johns Hopkins University Bayview Medical Center, Baltimore, MD.
02/19/10	Presenter, patients and caregivers, “Sleeping, Eating and Bathroom Issues in Dementia,” Baltimore Commissions on Aging and Retirement Education Caregiver Conference, Baltimore, MD.
05/15/13	Presenter, Korean seniors, Waxter Wisdom Memory Loss Presentation, Greenmount Senior Center, Baltimore, MD

07/25/14	Presenter, caregivers, “Driving Issues in Dementia,” Caregiver Education Seminar, the Johns Hopkins Memory and Alzheimer’s Treatment Center, Baltimore, MD.
11/08/14	Presenter, patients and caregivers, “Future Directions in Alzheimer’s Disease Care and Research,” Journey to Hope Conference, Johns Hopkins University Bayview Medical Center, Baltimore, MD.
10/23/15	Presenter, postdoctoral fellows, “Diagnosing Delirium at Home” Caregiver Education Seminar, Johns Hopkins University, Department of Psychiatry and Behavioral Sciences, Baltimore, MD.
01/30/14	Instructor, postdoctoral fellows, “Helping the Patient with Dementia Decide When and How to Stop Driving,” Geriatric and Neuropsychiatric noon seminar. Johns Hopkins University School of Medicine, Baltimore, MD.
05/08/15	Instructor, postdoctoral fellows, “3D CAM” Geriatric and Neuropsychiatric noon seminar. Johns Hopkins University School of Medicine, Baltimore, MD.
01/11/16	Presenter, biomarker researchers at the Johns Hopkins University, “Standardization of Biomarkers,” Johns Hopkins Alzheimer’s Disease Research Center Workgroup on Modeling Biomarkers, Johns Hopkins University, Baltimore, MD.

Mentoring

Pre-doctoral Advisees/Mentees

05/07 – 07/07	Amanda Smith, MD, medical student, Creighton University School of Medicine, Omaha, NE, present position – attending physician, Pediatric Partners, Bel Air, MD.
07/07 – 08/07	Julie King, MD, medical student, Johns Hopkins University School of Medicine, Baltimore, MD, present position – attending physician, Pavilion Pediatrics, Johns Hopkins at Green Spring Station, Lutherville-Timonium, MD; publication - manuscript # 4
06/09 – 08/09	Katherine Abalos, MD, medical student, University of Virginia, Charlottesville, VA, present position – attending physician, Beth Israel Deaconess Hospital, MA; poster presentation at the 2010 Annual Scientific Meeting, American Geriatrics Society (poster #10)
07/10 – 08/10	Daniel Parker, MD, medical student, Eastern Virginia Medical School, Norfolk, VA, present position – Internal medicine resident, Eastern Virginia Medical School, VA; Award - Presidential Poster Session, 2011 Annual Scientific Meeting, American Geriatrics Society, publication – manuscript #9

06/11 – 07/11	Carly Fabrizio, medical student, Rowan University, New Jersey School of Osteopathic Medicine, NJ; poster presentation at the 2012 Annual Scientific Meeting, American Geriatrics Society (poster #14)
06/12 – 08/12	Cathy Chen, undergraduate summer research student, Princeton University, Princeton, NJ, present position - 2nd year Medical student, University of Mississippi School of Medicine, Jackson, MS; publication - manuscript #11
06/12 – 07/12	Shayna Shackford, medical student, University of New England in Maine, Biddeford, ME; Award - Presidential Poster Session, 2013 Annual Scientific Meeting, American Geriatrics Society (poster #17)
06/14 – 08/14	Jessica Zimmerman, medical student, Eastern Virginia Medical School, Norfolk, VA, current position - medical student, Eastern Virginia Medical School; poster presentation at the 2015 Annual Scientific Meeting, American Geriatrics Society (poster #21)
06/15 – present	Megan Donnelly, undergraduate student, Department of Neuroscience in the Krieger School of Arts and Sciences, Johns Hopkins University, Baltimore, MD.
06/15 – 08/15	Samantha Mayhew, medical student, University of Cincinnati College of Medicine, Cincinnati, OH; Abstract accepted for the 2016 Annual Scientific Meeting, American Geriatrics Society (poster #31)

Post-doctoral Advisees/Mentees

10/11 – 06/14	Ying Liu MD, PhD, Senior Research Specialist, Department of Pathology, the Johns Hopkins University School of Medicine, Baltimore, MD, present position - Assistant Professor, Department of Neurology, the Johns Hopkins School of Medicine, Baltimore, MD; publication – manuscript # 6
02/12 – 04/14	Tolulope Fafowora, MD MBA, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD; publication - manuscript # 11
07/13 – 06/14	Monica Sandoval, MD, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD, present position – attending physician, Greater Baltimore Medical Center, Baltimore, MD
07/13 – 06/14	Jessica Lee, MD MS, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD, present position –Assistant Professor, Geriatrics and Palliative Medicine, The University of Texas

Health Sciences Center at Houston, Houston, TX; publication – manuscript #14

07/13 – present	Halima Amjad MD MPH, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD, currently postdoctoral fellow, the Johns Hopkins School of Medicine; publication – editorial #1.
02/14 – 06/15	Olivia Nirmalasari MD, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD, present position – attending physician, Providence ElderPlace PACE (Program of All Inclusive Care for the Elderly); poster presentation at the 2015 Annual Scientific Meeting, American Geriatrics Society (poster #20)
07/14 – 06/15	Jennifer Gabbard MD, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD, present position – Assistant Professor in Section of Gerontology and Geriatrics; Associate Program Director of Hospice and Palliative Medicine, Wake Forest University School of Medicine. Winston Salem, North Carolina; publication - web publication #3
07/14 – present	Stefan David MD, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD; publication - web publication #3
07/14 – present	Mia Yang MD, Postdoctoral fellow, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD.
11/14 – present	Sara Mamo AuD PhD, Postdoctoral fellow, Department of Otolaryngology-Head and Neck Surgery, the Johns Hopkins School of Medicine, Baltimore, MD, present position – Instructor, Department of Otolaryngology-Head and Neck Surgery, the Johns Hopkins School of Medicine, Baltimore, MD; publications – review articles #2 and 3; awards - New Investigator Research Grant, American Academy of Audiology
12/14 – present	Aisha Harun MD, Resident, Department of Otolaryngology-Head and Neck Surgery, the Johns Hopkins School of Medicine, Baltimore, MD; Award - the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNSF) Resident Research Grant; poster accepted for the Combined Otolaryngology Spring Meetings (COSM) (posters #30,

31)

07/15 – present Ariel Green, MD, MPH, Assistant Professor, Department of Medicine, Division of Geriatric Medicine and Gerontology, the Johns Hopkins School of Medicine, Baltimore, MD

Educational Program Building/Leadership

2007 – 2008 Associate Program Director, Medical Student Training in Aging Research.

2007 – present Member, Application Selection Committee, Medical Student Training in Aging Research.

2010 – 2013 Member, Planning Committee, Update on the Treatment of Alzheimer's Disease and Related Disorders (CME).

2011 – present Member, Medical Student Training in Aging Research (MSTAR) Application Selection Committee, Subcommittee for Ensuring Diversity, Johns Hopkins University School of Medicine.

2011 – present Director (2014-present), Co-director (2011-2014), Fellowship Professional Development Series, Johns Hopkins University School of Medicine

2012 – present Faculty Director, Johns Hopkins Division of Geriatric Medicine and Gerontology Fellowship Dementia Morning Report, Johns Hopkins University School of Medicine.

RESEARCH ACTIVITIES

Research Program Building/Leadership

2012 – present Chair, Adverse Event Consensus Panel, ADvance Clinical Study. In my capacity, I am responsible for leading clinical events committee (CEC) composed of a geriatrician, neurologist and a neurosurgeon for the ADvance Clinical Study.

2015 – present Co-leader, Dementia Research Group, Division of Geriatrics and Gerontology. In my capacity, I am responsible for co-mentoring postdoctoral fellows and junior faculty who are interested in dementia research.

Inventions, Patents, Copyrights

02/20/15 Oh E, Craft S, Lyketsos C. Methods for the identification, assessment, prevention, and treatment of neurological disorders and diseases. #62/118887

Clinical Studies

Current
Principal Investigator

2008 – present Oral Glucose Tolerance Test for Alzheimer's Disease

JHMI Protocol Number NA_00014837

Role: Principal Investigator

2011 – present Cerebrospinal fluid cytokines as biomarkers for delirium following hip fracture repair in elders

JHMI Protocol Number NA_00017021

Role: Principal Investigator

2013 – present Therapeutic effects of intranasally-administered insulin adults with amnestic mild cognitive impairment (aMCI) or mild Alzheimer's disease (AD) ADC-046-INI

JHMI Protocol Number NA_00014837

Role: Principal Investigator

2014 – present Targeted needs assessment for perioperative considerations for delirium prevention and management in elderly patients undergoing non-cardiac surgery.
JHMI Protocol Number IRB00053099
Role: Principal Investigator

2015 – present Prevalence of age related hearing loss among vulnerable older adults with cognitive impairment
JHMI Protocol Number IRB00064169
Role: Principal Investigator

2016– present Imaging in Dementia-Evidence for Amyloid Scanning (IDEAS) study
JHMI Protocol Number IRB00090317
Role: Principal Investigator

Co-Investigator

2009 – present Serotonin Modulation in Mild Cognitive Impairment

JHMI Protocol Number NA_00026190

Role: Co-Investigator

2011 – present A strategy to reduce the incidence of post-operative delirium in elderly patients

JHMI Protocol Number NA_00041873

Role: Co-Investigator

2011 – present Insulin Resistance in Late-Life Depression

JHMI Protocol Number NA_00066410

Role: Co-Investigator

2012 – present Advance Clinical Study
JHMI Protocol Number
Role: Medical Monitor

2013 – present 3T MRI imaging of dementia patients during clinical care
JHMI Protocol Number NA_00024337
Role: Co-Investigator

2013 – present Alzheimer's disease anti-inflammatory prevention trial (ADAPT)
JHMI Protocol Number NA_00041709
Role: Co-Investigator

2013 – present Insulin resistance in late-life depression
JHMI Protocol Number NA_00066410
Role: Co-Investigator

2014 – present Providing Hearing Health Care to Patients with Cognitive Impairment
JHMI Protocol Number IRB00036007
Role: Co-Investigator

2014 – present Skin biopsy for peripheral neuropathy
JHMI Protocol Number IRB00036876
Role: Co-Investigator

2014 – present Investigation of vestibular reflexes
JHMI Protocol Number IRB00035749
Role: Co-Investigator

2015 – present BDPP Treatment for Mild Cognitive Impairment (MCI)and prediabetes
JHMI Protocol Number IRB00000062802
Role: Co-Investigator

2015 – present MIND: An RCT of care coordination for community-living persons with dementia
JHMI Protocol Number IRB00041744
Role: Co-Investigator

2015 – present Comprehensive home-based dementia care coordination for Medicare-Medicaid Dual Eligibles in Maryland
JHMI Protocol Number IRB00054802

Role: Co-Investigator

2015 – present Improving Communication for Persons with Dementia and Hearing Loss
JHMI Protocol Number IRB00071067
Role: Co-Investigator

<u>Previous</u>
Principal Investigator

2011 – 2013 Examination of dementia patients and functional outcome

JHMI Protocol Number NA_00051361

Role: Principal Investigator

2010 – 2015 Alzheimer's Disease Cerebrospinal Fluid (CSF) Biomarker Study

JHMI Protocol Number NA_0035050

Role: Principal Investigator

Co-Investigator

2007 – 2010 A Double-Blind, Randomized, Placebo-Controlled, Dose Escalating Study to Evaluate the Safety, Tolerability, and Immunogenicity of V950 Formulated on Aluminum-Containing Adjuvant with or without Iscomatrix in Patients with Alzheimer's Disease

JHMI Protocol Number NA_00009297

Role: Co-Investigator

2008 – 2010 A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Eighteen Months of Treatment with PF-04494700 (TTP488) in Participants with Mild to Moderate Alzheimer's Disease

JHMI Protocol Number NA_00016662

Role: Co-Investigator

2008 – 2010 Effect of γ-Secretase Inhibition on the Progression of Alzheimer's Disease: LY450139 versus placebo

JHMI Protocol Number NA_00018175

Role: Co-Investigator

2008 – 2010 Phase III, Multicenter, Randomized, Double-Blind, Placebo Controlled, Parallel-Group, Efficacy and Safety Trial of Bapineuzumab (AAB-001, ELN 115727) in Patients with Mild or Moderate Alzheimer's Disease Who are Apolipoprotein E4 Carriers and Non-carriers

JHMI Protocol Number NA_00018175

Role: Co-Investigator

ORGANIZATIONAL ACTIVITIES

Institutional Administrative Appointments

2001 – 2002 Member, House Staff Evaluation Committee, Department of Medicine, University of Illinois at Chicago

2001 – 2002 Member, House Staff Council, Department of Medicine, University of Illinois at Chicago

2001 – 2002 Member, Education Committee, Department of Medicine, University of Illinois at Chicago

2005 – 2007 Member, Diagnostic Consensus Panel, Alzheimer's Disease Research Center, Johns Hopkins University

2008 – 2010 Committee Member, Women's Task Force, Johns Hopkins University School of Medicine

2010 – 2013 Member, Planning Committee for the Update on the Treatment of Alzheimer's and Related Disorders, Peer Reviewer for Conflict of Interest

2011 – 2012 Committee Member, SMART Strategic Goal: Building Community Committee, Division of Geriatric Medicine and Gerontology, Johns Hopkins University

Editorial Activities

Editorial Board Appointments

2011 Associate Editor, the Journal of Alzheimer's disease

Journal Peer Review Activities

2008 – present	Abstract reviewer, Neurological and Behavioral Sciences abstract review category, American Geriatrics Society Annual Scientific Meeting
2009	Reviewer, the Journal of Alzheimer's disease
2011 – present	Reviewer, the Journal of American Geriatrics Society
2012 – present	Protocol reviewer, Institute for Clinical and Translational Research (ICTR) Clinical Research Unit (CRU)
2012 – present	Reviewer, International Psychogeriatrics
2012 – present	Reviewer, PLOS One
2013 – present	Reviewer, Johns Hopkins Alzheimer's Disease Research Center pilot grants
2014	Reviewer, Alzheimer's Research and Therapy
2014	Reviewer, Reichel's Care of the Elderly: Clinical Aspects of Aging (7th edition), Cambridge Press
2015	Reviewer, Journal of Gerontology: Medical Sciences
2015	Reviewer, Alzheimer's & Dementia: The journal of the Alzheimer's Association
2016 – present	Reviewer, International Journal of Geriatric Psychiatry

Other Peer Review Activities

None

Professional Societies

1996 – present	Member, Christian Medical & Dental Associations
2001 – present	Member, American Geriatrics Society
2006 – present	Member, Society for Neuroscience
2006 – present	Member, Special Interest Group (SIG) on Clinical Research in Dementia, American Geriatrics Society
2008 – present	Steering Committee Member, American Geriatrics Society Research Junior Faculty SIG Steering Committee

2010 – present	Member, International College of Geriatric Psychoneuropharmacology
2010 – present	Member, Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART)
2011 – present	Member, American Delirium Society
2012 – present	Member, European Delirium Society
2013 – present	Executive Committee Member, International Society to Advance Alzheimer's Research and Treatment (ISTAART) Professional Interest Area (PIA) Perioperative Cognition
2014 – present	Member, American Geriatrics Society Research Junior Faculty Special Interest Group (SIG) Research Methods Sub-committee.
2015 – present	Member, American Delirium Society Research Committee
2015 – present	Vice Chair, International Society to Advance Alzheimer's Research and Treatment (ISTAART) Professional Interest Area (PIA) Perioperative Cognition
2015 – present	Perioperative Cognition Professional Interest Area (PIA) nomenclature consensus working group

RECOGNITION

Awards and Honors

1990	John A. Hartford Foundation Fellowship in Geriatric Medicine
1991	de Kiewiet Summer Research Scholarship
1992	Okayama University International Exchange Scholarship
1995	National Institute of Health Summer Internship Program, National Institute of Neurological Disorders and Stroke (NINDS)
2002 – 2005	National Institute on Aging Research Training (T32) in Gerontology and Geriatric Medicine
2003	Technical Assistance Workshop, National Institute on Aging
2005	Summer Institute on Aging Research, National Institute on Aging
2006	Presidential Poster Session, Annual Scientific Meeting, American Geriatrics Society (Also received awards in 2007, 2010, 2011, 2013)
2009 – 2011	The Rosalinde and Arthur Gilbert Foundation/AFAR New Investigator Award in Alzheimer's disease
2010	Merck New Investigator Award

2010 – 2011	Johns Hopkins Clinical Research Scholars Junior Faculty KL2 Award
2010	International College of Geriatric Psychoneuropharmacology Junior Investigator Award
2011	Early Career Women Faculty Professional Development Seminar, Association of American Medical Colleges (AAMC) (competitive selection)
2012	Johns Hopkins Emerging Women's Leadership Program inaugural cohort (competitive selection)
2012	Career Development Award recipient (K23), National Institute on Aging
2013	Johns Hopkins Junior Faculty Leadership cohort (competitive selection)
2013	Excellence in Teaching Award, Johns Hopkins School of Medicine, Division of Geriatric Medicine and Gerontology
2014	American Geriatrics Society (AGS)/National Institute on Aging (NIA) U13 Conference Series attendee (Delirium in Older Adults: Finding Order in the Disorder) (competitive selection)
2014	CEDARTREE Second Annual Delirium Bootcamp Travel Grant Recipient (competitive selection)
2015	Johns Hopkins Leadership Program for Women Faculty (competitive selection)
2016	Advanced Research Institute in Geriatric Mental Health Scholar award

Invited Talks, Panels

JHMI / Regional

05/16/09	Presenter, Johns Hopkins University Dementia Retreat, "Attenuation of Monoaminergic Neurodegeneration by Immunotherapy," Baltimore, MD
03/06/10	Presenter, 3rd Annual Billie Showers Research Symposium, "Alzheimer's and Diabetes, Is There a Connection?," Washington DC
03/24/10	Presenter, Welch Center for Prevention, Epidemiology and Clinical Research, the Diabetes and Obesity Group, "Insulin Resistance and Alzheimer's disease – Is there a Connection?," Baltimore, MD

09/19/11	Presenter, Johns Hopkins University Delirium Consortium, "Biomarkers of Delirium," Baltimore, MD
09/28/11	Presenter, Willow Valley Retirement Community, "Journey of Hope: Perspectives and Progress on the Alzheimer's Front," Lancaster, PA
11/08/11	Presenter, Johns Hopkins Health Care, "Dementias of Diabetes," Glen Burnie, MD
11/02/12	Presenter, Department of Medicine Grand Rounds, Johns Hopkins University, "CSF Biomarkers of Postoperative Delirium in Hip Fracture Patients," Baltimore, MD
06/05/13	Presenter, Abramson Center for Jewish Life, "Successful Aging: Preventing Your Risk for Developing Dementia," North Wales, PA
03/28/14	Panelist, Professional Development Office & Office of Faculty Development, Johns Hopkins Medical Institutions, "Writing Successful K application: Beyond the Basics," Baltimore, MD
02/04/15	Grand Rounds Speaker, Copper Ridge Institute, "Hearing Loss and Cognitive Impairment," Sykesville, MD
03/27/15	Grand Rounds Speaker, MedStar Harbor Hospital, "Delirium and Dementia," Baltimore, MD
04/20/15	Presenter, Johns Hopkins University Delirium Consortium, "Sex Differences in Hip Fracture Surgery Preoperative Risk Factors of Delirium and Postoperative Outcomes," Baltimore, MD
01/11/16	Presenter, Johns Hopkins Alzheimer's Research Center Workgroup on Modeling Biomarkers, "Standardization of Biomarkers," Baltimore, MD
03/21/16	Presenter, Johns Hopkins University Dementia Consortium, "Oral Glucose Tolerance Test as a Biomarker Tool for Alzheimer's disease

National

11/20/03	Presenter, National Institute on Aging, "Development of Serum Assays for Diagnosis of Pre-Clinical Alzheimer's Disease." Technical Assistance Workshop, San Diego, CA
10/19/04	Presenter, The University of Chicago, Section of Geriatrics, "Passive Immunization and Alzheimer's disease," Chicago, IL
06/09/05	Presenter, American Association of Neuropathologists 2005 Annual Meeting, "Passive immunization with monoclonal antibody Aβ 1-11 in transgenic mouse models of Alzheimer's disease,"Washington DC

05/02/09 Presenter, American Geriatrics Society 2009 Annual Meeting Paper Session, “Immunotherapy Attenuates Monoaminergic Neurodegeneration in Transgenic Mice,” Chicago, IL

06/08/10 Presenter, The Rosalinde and Arthur Gilbert Foundation/AFAR Meeting, “Oral Glucose Tolerance Test for Alzheimer’s disease Biomarker Development,” Santa Barbara, CA

11/08/12 Presenter, Department of Anesthesiology & Critical Care, Weekly Research In Progress Seminar, Perelman School of Medicine, University of Pennsylvania, “Using CSF biomarkers of AD to Identify Patients at Risk for Postoperative Delirium,” Philadelphia, PA

11/23/13 Presenter, Symposium: Persons With Cognitive Impairment in Studies After Hip Fracture: What Do We Know and What Can We Do? Annual Meeting, the Gerontological Society of America (GSA), “Dementia and Delirium after Hip Fracture: In-Hospital Associations and Outcomes,” New Orleans, LA

05/16/14 Presenter, Report from the 2014 U13 AGS-NIA Conference - Delirium in Older Adults: Finding Order in the Disorder, Annual Meeting of the American Geriatrics Society, “Delirium and Dementia,” Orlando, FL

05/16/15 Presenter, American Geriatrics Society 2015 Annual Meeting, Geriatrics Consultative Services Special Interest Group (SIG), “Geriatricians as Consultants for Cognitive Impairment,” Oxon Hill, MD

03/29/16 Presenter, University of Illinois at Chicago, Department of Medicine, Grand Rounds, “Current and Future Treatments for Alzheimer’s disease,” Chicago, IL
Presenter, University of Illinois at Chicago, Department of Medicine and Geriatric Medicine Fellowship Lecture, “Interrelationship of Delirium and Dementia,” Chicago, IL

03/31/16 Presenter, University of Chicago, Section of Geriatrics and Palliative Medicine Grand Rounds, “Postoperative delirium,” Chicago, IL

International

08/06/10 Presenter, XV Symposium Internacional de Geriatria y Gerontologia, “Advances in the Dementias; Mild Cognitive Impairment,” Guadalajara, Mexico

09/15/10 Presenter, International College of Geriatric Psychoneuropharmacology, Junior Investigator Award Presentation, “Neopterin Levels in amnestic MCI and Alzheimer’s disease,” Athens, Greece

07/13/13	Presenter, Alzheimer’s Association International Conference (AAIC), Anesthesiology Symposium: “Perioperative Management of Cognition,”Boston, MA
07/12/14	Presenter, Alzheimer’s Association International Conference (AAIC), Perioperative Cognition Professional Interest Area (PIA), Pre-conference Symposium, “Cognitive Recovery after Cardiac Surgery and the Role of Delirium,” Copenhagen, Denmark
08/10-16/14	Presenter, The Sino-US Academic Forum, The Second Hospital of Dalian Medical University, Medical Co-morbidities in Dementia Care, “Interrelationship of Delirium and Dementia; Treatments for Alzheimer’s disease,” Dalian, China
07/21/15	Presenter, Alzheimer’s Association International Conference (AAIC), Research Symposium, “Delirium and Its Sequelae,” Washington DC
09/04/15	Presenter, European Delirium Association, CSF studies in delirium research: lessons learned and future directions, “Standardization of Biomarkers,” London, United Kingdom

OTHER PROFESSIONAL ACCOMPLISHMENTS

Posters

1. Sakurai H, Oh E, Sano K, Tsuchiya T, Tsuda M. Induction of Novel DNA-Binding Activity in the Cerebellar Granule Cells Stimulated via Glutamate Receptors. 1st UBMB Conference, Biochemistry of Diseases, June 1, 1992.
2. Sakurai H, Oh E, Sano K, Tabuchi A, Tsuchiya T, Tsuda M. Induction of TRE Binding Activities Mediated by Glutamate Receptors and Its Regulation by Nitric Oxide (NO). Japanese Biochemical Society Meeting. December 9-12, 1992.
3. Khan A, Oh E, Weisman D, Lesky L. End-Of-Life Curriculum Development at a University Hospital. The Journal of Palliative Medicine, 2001; 4:4,533.
4. Oh, ES., Tucker S, Jankowsky J, Borchelt D,Troncoso J. Peripheral administration of monoclonal antibody as a diagnostic tool to detect soluble amyloid beta. J Am Geriatr Soc., 2005; 53, S19.
5. Oh E, Tucker S, Riudavets M, Borchelt D, Troncoso J. The Effect of Anti-amyloid beta Antibody 7B6 on Neuronal Cell Volume. J Am Geriatr. Soc. 2006:54.S156 (Selected for Presidential Poster Session).
6. Oh E, Tucker S, Smith A, Borchelt D, Troncoso J. Biotinylated anti-Aβ antibody as a tool to diagnose pre-clinical Alzheimer’s disease (AD). 36th Annual Meeting of the Society for Neuroscience, Oct, 2006
7. Oh ES, Tucker S, Borchelt D, Troncoso J. Biotinylated antibody as a tool to diagnose pre-clinical stages of Alzheimer's Disease (AD). J Am Geriatr. Soc. 2007:55.S163 (Selected for Presidential Poster Session).

8. Oh E, Tucker S, Borchelt D, Troncoso J. Use of a Biotinylated Anti-Aβ Antibody to Diagnose Preclinical Alzheimer's Disease. Alzheimer's Association Prevention Conference. Alzheimer's & Dementia. 2007:3:3 S2 114
9. Oh E, Savonenko A, Fangmark-Tucker S, Rudow G, Xu G, Borchelt D, Troncoso J. The Neurotrophic Effects of Amyloid Precursor Protein (APP) on Cortical Neuronal Volumes of Transgenic Mouse Models. 37th Annual Meeting of the Society for Neuroscience, Nov 5, 2007 (Poster Presentation).
10. K. Abalos, Y. Liu, G. Rudow, J. Troncoso, E. Oh. Attenuation of Catecholaminergic Axons in Asymptomatic Alzheimer's disease (ASYMAD). J Am Geriatr Soc. 2010:58.S180-181.
11. Oh ES, Mielke MM, Rosenberg PB, Jain A, Fedarko N, Lyketsos CG, Mehta P. Comparison of Conventional ELISA with Electrochemiluminescence Technology for Detection of Amyloid-beta (Aβ) in Plasma. J Am Geriatr.Soc. 2010:58.S121 (Selected for Presidential Poster Session).
12. Oh ES, Leoutsakos J, Mielke, MM, Rosenberg PB, Troncoso JC, Elahi D, Green PS, Lyketsos, CG, and S. Craft. Oral glucose tolerance test for Alzheimer's disease biomarker development. The Rosalinde and Arthur Gilbert Foundation/AFAR Grantee Meeting. June 8, 2010. Santa Barbara, CA.
13. Oh ES, Parker D, Mielke MM, Rosenberg PB, Jain A, Fedarko NS, Lyketsos CG. Plasma Neopterin Levels in aMCI and AD. International Congress of Geriatric Neuropsychopharmacology Meeting, September 17, 2010. Athens, Greece
14. Fabrizio C, Lyketsos CG, Oh ES. Improvement in Functional Independence Measure (FIM) scores of dementia patients on a Medical Psychiatry Unit. J Am Geriatr.Soc. 2012:60.C138.
15. Esther S. Oh, Paul B. Rosenberg, Hochang B. Lee, Allison E. Carlson, Richard J. O'Brien, Constantine G. Lyketsos, Frederick E. Sieber, and Simon C. Mears (July 2012) Correlation of Cerebrospinal Fluid (CSF) Amyloid-β42 and Tau Levels with Postoperative Delirium Severity in Patients Undergoing Hip Surgery, Alzheimer's Association International Conference on Alzheimer's Disease. July 16, 2012. Vancouver, Canada
16. Esther S. Oh, Paul B. Rosenberg, Hochang B. Lee, Allison E. Carlson, Richard J. O'Brien, Constantine G. Lyketsos, Frederick E. Sieber, and Simon C. Mears (July 2012) Correlation of Cerebrospinal Fluid (CSF) Amyloid-β42 and Tau Levels with Postoperative Delirium Severity in Patients Undergoing Hip Surgery, 14th Annual ACCM Research Day, December 10, 2012 Baltimore, MD.
17. S. Shackford, PB. Rosenberg, ES Oh. The Effects of Cognitive Impairment on Rehabilitation Outcomes in a Medical Psychiatric Unit. J Am Geriatr.Soc. 2013:61.S98 (Selected for Presidential Poster Session).
18. Yokoi Y, Misal M, Oh E, Bellantoni M, J. Mohler, Rosenberg B. Benzodiazepine discontinuation and patient outcome in a chronic geriatric medical/psychiatric unit: A retrospective chart review. J Am Geriatr.Soc. 2013:61.S65
19. Sara Mamo, Carrie Nieman, Olivia Nirmalasari, Esther Oh, Frank Lin. Geriatric clinic based hearing intervention for persons with dementia. American Auditory Society Scientific and Technology Meeting March 5-7, 2015.
20. Nirmalasari O, Mamo S, Neiman C, McNabney M, Simpson A, Albert M, Lyketsos C, Oh E, Lin F. Reducing the symptom burden of cognitive impairment through a clinic-delivered hearing care intervention. J Am Geriatr Soc. 2015:63.S225.
21. Buford-Blair J, Nirmalasari O, Mamo S, Neiman C, Simpson A, Lyketsos C, Lin F, Oh E. Prevalence of hearing loss in a Memory clinic, J Am Geriatr Soc. 2015:63.S273-274.

22. Gabbard J, David S, Oh E, McNabney M. Target needs assessment for perioperative delirium consideration in elderly patients undergoing orthopedic surgery, J Am Geriatr Soc. 2015:63.S193.
23. Gabbard J, David S, Oh E, McNabney M. Developing a curriculum for general surgery residents on postoperative delirium: considerations in older adults undergoing surgery, Annual Meeting of the American Delirium Society June 1-2, 2015.
24. Mamo S, Nirmalasari O, Neiman C, Simpson A, Oh E, Lin F. A clinic-based intervention to address hearing loss and communication difficulties in patients with dementia and their caregivers. Alzheimer's Association International Conference July 22, 2015.
25. Sara K. Mamo, Olivia Nirmalasari , Carrie Nieman, Allison Simpson, Esther Oh, Frank Lin. Hearing intervention to improve communication for persons with dementia and their caregivers Submitted Gerontological Soceity of America 2015.
26. Constantine G. Lyketsos, Gwenn Smith, Lisa Fosdick, Jeannie-Marie Leoutsakos, Cynthia Munro, Esther Oh, Kristen Drake, Paul B. Rosenberg, William S. Anderson, Stephen Salloway, Cara Pendergrass, Anna Burke, David A. Wolk, David F. Tang-Wai, Francisco A. Ponce, Wael F. Asaad, Marwan Sabbagh, Michael S. Okun, Gordon Baltuch, Kelly D. Foote, Steven D. Targum, and Andres M. Lozano. Deep brain stimulation targeting the fornix for mild Alzheimer's disease: initial results of the Advance randomized controlled trial. Developing Topics, Alzheimer's Association International Conference July 22, 2015
27. Wong D, Borroni E, Kuwabara H, George N, Rosenberg P, Lyketsos C, Resnick S, Thambisetty M, Brasic J, Gapasin L, Willis W, Knust H, Guerard M, Belli S, Muri D, Carey T, Bedding A, Wandel C, Hansrod T, Honer M, Moghekar A, Boess F, Albert M, Shaya E, Oh E, Ostorwitzki S, Dannais R, Comley R. First In-Human PET study of 3 novel tau radiopharmaceuticals: [11C]RO6924963, [11C]RO6931643, and [18F]RO6958948. Developing Topics, Alzheimer's Association International Conference July 22, 2015
28. Sara K. Mamo, Olivia Nirmalasari, Carrie Nieman, Matthew McNabney, Esther Oh, Frank Lin. Aural rehabilitation in geriatric clinic and group care settings. The 7th Biennial National Center for Rehabilitative Auditory Research (NCRAR) Conference, September 16-18, 2015
29. Fornix deep brain stimulation for Alzheimer's disease: results of the Multi-center Advance Trial. Oral communication, Clinical Trials on Alzheimer's Disease (CTAD 2015), November 5-7, 2015
30. Aisha Harun, Robin Bigelow, Esther Oh, Yuri Agrawal. The association between vestibutlar function and visuospatial ability in individuals with dementia. Association of Research in Otolaryngology (ARO), February 20-24, 2016
31. Aisha Harun, Robin Bigelow, Esther Oh, Yuri Agrawal. Vestibular function is impairment in individuals with dementia. Combined Otolaryngology Spring Meetings (COSM), May 18-22, 2016 (accepted)
32. Samantha Mayhew, Sara Mamo, Matthew McNabney, Frank Lin, Esther Oh. Communication between caregivers and participants in Program of All-Inclusive Care for the Elderly (PACE), 2016 Annual Meeting of the American Geriatrics Society, May 2016 (accepted)
33. Aisha Harun, Esther Oh, Robin Bigelow, Yuri Agrawal. Vestibular and Visuospatial Function in Individuals with Dementia, American Academy of Head and Neck Surgery (AAO-HNSF), (submitted)

Oral/Podium Presentations (Abstracts)

34. Oh ES, Tucker SM, Rudow GL, Jankowsky JL, Borchelt DR, Troncoso JC. Passive immunization with monoclonal antibody Aβ 1-11 in transgenic mouse models of Alzheimer's disease. American Association of Neuropathologists 2005 Annual Meeting. June 9-12, 2005. (Selected for Podium presentation)